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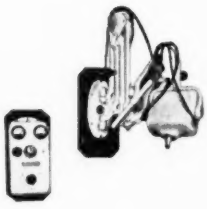

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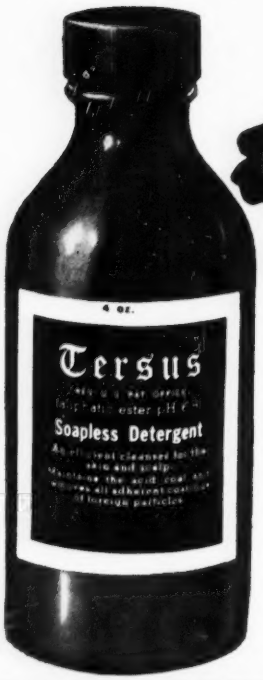

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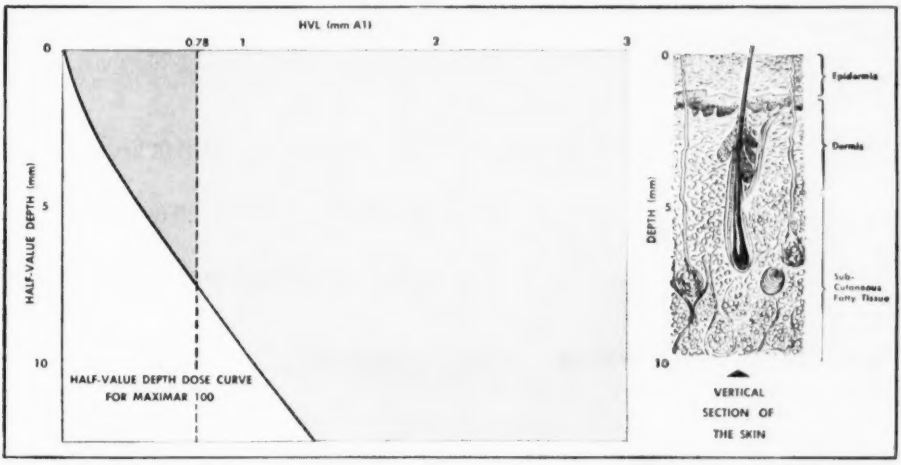

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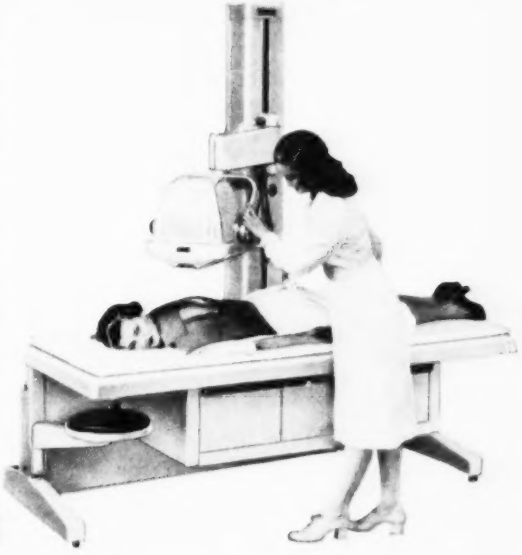

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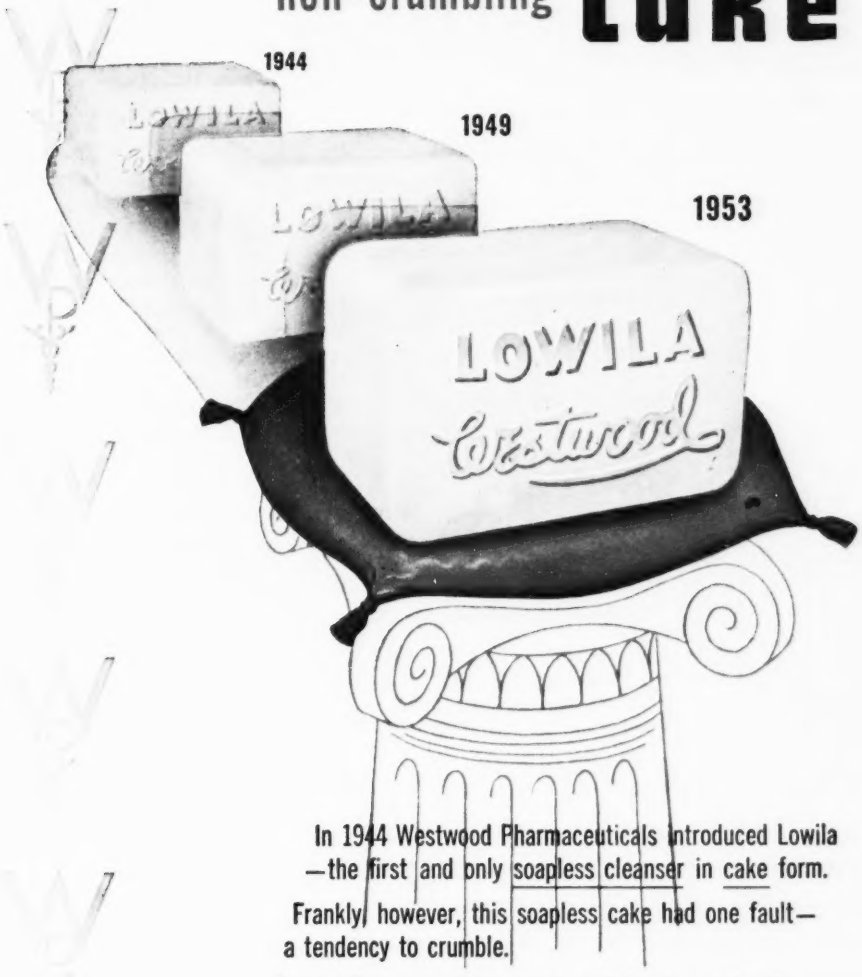

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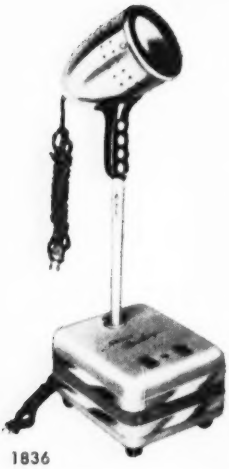

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VOLUME 68 NOVEMBER 1953 NUMBER 5

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CONTRIBUTIONS TO THE STUDY OF PEMPHIGUS

JOSEPH G. BRENNAN, M.D.
ROCHESTER, MINN.

A COMPREHENSIVE survey of the records of patients seen at the Mayo Clinic who had probable diagnoses of pemphigus vulgaris and other serious bullous dermatoses was made. It was determined from histologic study that a good correlation was present between the phenomenon of acantholysis and the subsequent course of patients who died of pemphigus vulgaris.[1]

During the past three years, special studies have been made at the Clinic with regard to patients who had pemphigus and other severe bullous disorders; these studies have included comprehensive clinical examinations, routine laboratory tests, and, especially, histologic, cytologic, bacteriologic, and chemical investigations of the bullae as they occurred naturally and were produced artificially. The data so accumulated have thrown light on the pathologic physiology of the formation of bullae.

These studies will be presented in two parts: (1) cytology of spontaneous bullae and (2) observations on the formation of artificial bullae.

CYTOLOGY OF SPONTANEOUS BULLAE [2]

Auspitz,[3] in 1881, classified dermatologic entities according to their histologic features. He formulated nine classes and included acantholysis in the third subdivision of his seventh class; the latter included pemphigus. He coined the term "acantholysis," meaning destruction of the prickles or melting away of the intercellular bridges. This concept was strongly opposed by his contemporaries, especially by Hebra,[4] who stated that if the concept of Auspitz were true, then pemphigus would be diagnosed in many cases. This idea, therefore, died with Auspitz.

Fellow in Dermatology and Syphilology, Mayo Foundation.

Awarded first prize in the Third Annual Essay Contest of the American Dermatological Association, Inc., 1953.

Read at the meeting of that association at Lake Placid, N. Y., June 10, 1953.

Work was done in the Section of Dermatology, Mayo Clinic, with the assistance of Dr. P. A. O'Leary, Dr. Hamilton Montgomery, Dr. L. A. Brunsting, and Dr. R. R. Kierland; in the Section of Physiology with the assistance of Dr. H. E. Essex; in the Section of Bacteriology with the assistance of Dr. F. R. Heilman; in the Section of Biochemistry with the assistance of Mr. B. F. McKenzie, and in the Section of Photography with the assistance of Mr. L. B. Nichols.

1. Brennan, J. G., and Montgomery, H.: Pemphigus and Other Bullous Dermatoses: Correlation of Clinical and Pathologic Findings. J. Invest. Dermat.

2. This part of the article is an abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

3. Auspitz, H.: System der Hautkrankheiten, Vienna, Braumüller, 1881, Vol. 4.

4. Hebra, H.: System der Hautkrankheiten von Dr. Heinrich Auspitz, reprinted from Wiener Medizinische Blätter, Nos. 1, 2, 3, and 4, 1881, Vienna, L. Bergmann u. Compaznie, 1881.

It was not until 1936 that this theory was revived by Darier and Civatte and their group.[5] These authors insisted that certain bullous dermatoses, chief among which was pemphigus vulgaris, could be diagnosed with certainty. In 1943, Civatte [6] again emphasized that the bulla of pemphigus was always within the epidermis and that it displayed characteristic histologic features which allowed differentiation from dermatitis herpetiformis and erythema multiforme.

In a series of papers, Tzanck and Tzanck and Aron-Brunetière [7] demonstrated that pemphigus could be differentiated from other bullous dermatoses by means of scrapings taken from the floor of spontaneous bullae. They came to the conclusion that only pemphigus gave a "typical, constant, and specific picture" never encountered in any other condition. Of special significance were plaques of altered epithelial cells, rounded and devoid of their means of attachment; this appearance constitutes acantholysis, which is the characteristic change of pemphigus.

The acantholytic cell presents the following characteristics: The cell as a whole is enlarged and spherical; its periphery is intensely basophilic, forming a halo at its edge. The nucleus is also spherical and enlarged; the nucleoli are prominent. Such changes give rise to the so-called Tzanck cell, which is diagnostic of pemphigus.

The work of Tzanck's group has been confirmed by numerous workers, including Civatte,[6] Cordero,[8] Rook and Whimster,[9] Nelemans,[10] Winer and Lipschultz,[11] Blank and Burgoon,[12] Santoianni,[13] Zoon and Mali,[14] Beerman and others,[15] and Brennan and others.[16]

---

5. Darier, J.; Civatte, A.; Flandin, C., and Tzanck, A.: Altérations des cellules malpighiennes, in Darier, J.; Civatte, A.; Flandin, C., and Tzanck, A.: Nouvelle practique dermatologique, Paris, Masson & Cie, 1936, Vol. 1, pp. 303-321.

6. Civatte, A.: Diagnostic histopathologique de la dermatite polymorphe douloureuse ou maladie de Duhring-Brocq., Ann. dermat. et syph. **3**:1-30 (Jan.-Feb.) 1943.

7. Tzanck, A.: Le cytodiagnostic immédiat en dermatologie, abstracted in Bull. Soc. franç. dermat. et syph. **57**:68 (Feb. 13) 1947; Un signe caractéristique de pemphigus, Gaz. med. de France **54**:619-620, 1947. Tzanck, A.: Bourgeois-Gavardin, and Aron-Brunetière, R.: Le cytodiagnostic immédiat en dermatologie, Ann. dermat. et syph. **8**:205-218 (May) 1948. Tzanck, A.; Sidi, E.; Melki, and Damoiseau: Cytodiagnostic immédiat dans un cas de pemphigus subaigu malin extensif, de localisation buccale, Bull. Soc. franç. dermat. et syph. **60**:388-389 (July 6) 1950. Tzanck, A.: Discussion sur la pemphigoide séborrhéique, ibid. **61**:355-356 (May *26, 27*) 1951.

8. Cordero, A. A. J.: Valor del citodiagnóstico en las dermatosis ampollares, Rev. argent. dermatosif. **31**:578-585 (July-Dec.) 1947.

9. Rook, A. J., and Whimster, I. W.: The Histological Diagnosis of Pemphigus, Brit. J. Dermat. **62**:443-446 (Nov.) 1950.

10. Nelemans, T. G.: Pemphigus vulgaris en dermatitis herpetiformis Duhring; een aetiologisch, histologisch en cytologisch onderzoek, The Netherlands, Te Assen Bij, 1951.

11. Winer, L. H., and Lipschultz, C. E.: Comparative Study of Histology and Cytology in Vesiculating Eruptions, A. M. A. Arch. Dermat. & Syph. **65**:270-290 (March) 1952.

12. Blank, H., and Burgoon, C. F.: Abnormal Cytology of Epithelial Cells in Pemphigus Vulgaris: A Diagnostic Aid, J. Invest. Dermat. **18**:213-221 (March) 1952.

13. Santoianni, G.: Cytology of Blisters According to Modern Methods: Bullous Dermatoses with Particular Interest in the Pemphigus Group, Ann. ital. dermat. sif. **5**:335-340 (Nov.-Dec.) 1951.

14. Zoon, J. J., and Mali, J. W. H.: Remarks on Cell-Diagnostics in Normal and Some Pathological Conditions of the Skin, Dermatologica **101**:145-153, 1950.

15. Beerman, H., and others: Symposium on Pemphigus and Bullous Dermatoses, in Conference on the Bullous Dermatoses, H. E. Michelson, Chairman, University of Minnesota, Nov. *21-22*, 1950.

(Footnote continued on next page)

Cytologic and histologic studies made by means of smears from the contents of spontaneous bullae, scrapings from the floors of bullae, biopsy specimens, and biopsy touch smears, all made from the same lesion, have been carried out for patients who had the following conditions: pemphigus vulgaris (11); pemphigus vegetans (1); pemphigus foliaceus (1); suspected pemphigus (7); bullous erythema multiforme (9); dermatitis herpetiformis (13); herpes gestationis (1); bullous eruption from intravenous use of mersalyl, or Salyrgan (1); vesicular eczema (3); tinea pedis with bullae on the feet (1); dyshidrosis (1); epidermolysis bullosa (2); burn with boiling oil (1); burn with hot lead (1); bullous lichen planus (1); bullous lymphoblastoma (2); porphyria (1); polymorphous light-sensitive eruption (1), and acute systemic bullous lupus erythematosus (1).

Scrapings, biopsy specimens, and biopsy touch smears obtained from patients who had the following conditions were examined: pemphigus vulgaris (2), pemphigus vegetans (1), pemphigus foliaceus (1), indeterminate oral lesion (1), indeterminate oral and vulvar lesions (2), dermatitis herpetiformis (2), familial benign chronic pemphigus (3), and bullous erythema multiforme (2).

Only scrapings and smears from the contents of bullae were made in studies of additional patients with the following conditions: dyshidrosis (4), tinea pedis (3), vesicular eczema (6), herpes progenitalis in a male (1), and bullous lichen planus of the penis with biopsy done elsewhere (1).

Only scrapings were made in studies of additional patients with the following conditions: indeterminate oral lesions (2) and bullous erythema multiforme in an infant (1).

Smears of Contents of Bullae.—Technique: An early spontaneous bulla was chosen; a small amount of alcohol was dropped over it, and the roof was pierced with a cataract knife. A wire loop was introduced into the cavity of the bulla, and a tiny drop of material was collected and smeared on a clean glass slide. The slide was waved in the air for quick drying; it was then stained at any convenient time. Wright's stain was used at first, but it was found that counterstaining according to Giemsa's method brought out nuclear characteristics much better. Eight slides were prepared in this fashion from each bulla examined; they represented the concentrated preparation. Two thin preparations were also made according to the usual technique used in making thin blood smears. Specimens were taken from various bullae in the same patient when possible. The following stains were used: Giemsa's, Gram's, Hotchkiss-McManus', aurmaine O (these preparations were examined microscopically by means of ultraviolet radiation), and Ziehl-Neelsen's.

Results: Smears of fluid from the bullae were diagnostic (Fig. 1*a*) in all cases of pemphigus vulgaris, in one case of pemphigus vegetans, and in one case of pemphigus foliaceus. By "diagnostic" is meant the presence of prickle cells undergoing pathologic changes. The prickle cell increases in size, becomes spherical, and loses its prickles, or its connections with neighboring cells. The cytoplasm becomes homogenous. The intercellular portions of the prickles are clumped at the periphery to form a dark areola of condensation at the edge of the cell. The nucleus is rounded, irregular, and increased in size; the nucleoli also are increased in size and are irregular. Vacuoles may be present and may be so large as to occupy the whole

16. Brennan, J. G., and others: Symposium on the Physiology and Pathology of Pemphigus, in Conference on the Bullous Dermatoses, H. E. Michelson, Chairman, University of Minnesota, Nov. 21-22, 1952.

nucleus and push its remains toward the nuclear edge. Nuclear debris, neutrophiles, lymphocytes, and eosinophiles are found in variable numbers. Some or all of these changes may be found in pemphigus vulgaris. However, the specific lesion is an altered, dead or dying, acantholytic cell, a cell that has lost its prickles because of the disease process and that displays specific nuclear and cytoplasmic changes. In four cases of pemphigus vulgaris, the studies had to be repeated several times before a definite conclusion was reached. In two cases of pemphigus vulgaris, the smears were definitely diagnostic before and during prolonged therapy with cortisone. Smears from lesions in the other bullous dermatoses were not diagnostic.

Scrapings from the Floors of Bullae and from Erosions of Skin and Mucous Membranes.—Technique: The roof of the bulla was partly removed with tiny scissors,

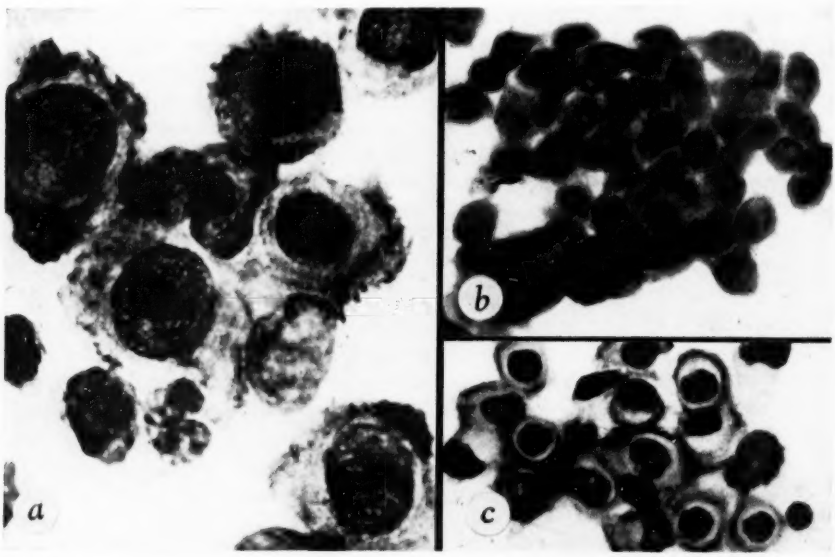

Fig. 1.—Spontaneous bullae of pemphigus vulgaris. (*a*) Fluid content; note Tzanck cells. (Wright counterstained with Giemsa; × 1,500.) (*b*) Scrapings from floor of bulla; note cluster of Tzanck cells. (*c*) Biopsy touch smear; note Tzanck cells. (*b* and *c*) Wright counterstained with Giemsa; × 650.)

and the floor, preferably at the edge, was scraped gently with a sharp No. 2 or No. 3 Buck's ear curet. Care was taken to prevent bleeding during the process. The scrapings were then smeared on four to six clean glass slides, fixed in absolute alcohol for 30 minutes or more, stained with hematoxylin and eosin or Wright's stain, and counterstained by Giemsa's method or with Masson's trichrome stain; a cover slip was then placed over the preparation.

Erosions of the skin and mucous membranes were scraped gently. Preparations stained by means of the Hotchkiss-McManus technique were studied to rule out fungous infection.

Results: Scrapings were diagnostic in all cases of pemphigus vulgaris (Fig. 1*b*), in one case of pemphigus vegetans, and in one case of pemphigus foliaceus. Scrapings from the indeterminate lesions limited to the mucous membranes were not diag-

nostic for pemphigus except in two cases. In one of these, oral lesions had been present for six months; in the other, clusters of Tzanck cells were found in oral and vulvar lesions that had been present for two months. In another case, study of material obtained from indeterminate lesions of the oral mucosa and stained by means of the Hotchkiss-McManus technique revealed mycelial forms of Candida albicans.

Scrapings from the two patients in whom burns were present disclosed numerous polymorphonuclear leucocytes, lymphocytes, and necrotic debris. Scrapings from the three patients who had familial benign chronic pemphigus showed acantholytic cells, as well as prickle cells that had retained some of their prickles. Some of the cells showed evidence of mitotic division.

Scrapings from lesions representing the remaining bullous dermatoses were not diagnostic; they disclosed varying numbers of polymorphonuclear leucocytes, lymphocytes, eosinophiles, and normal prickle cells with well-preserved prickles. The last-named cells had been forcibly scraped off during the procedure. The intercellular bridges that bind one prickle cell to another had been broken off by the forceful action of the curet. The term "acanthorhexis" is proposed to refer to this process of mechanical rupture of the intercellular bridges with consequent liberation of a prickle cell with its prickles still attached. Acanthorhexis is opposed to acantholysis, in that the latter represents destruction of the prickles by a disease process while the former represents rupture of the intercellular bridges produced mechanically during the scraping procedure.

Biopsy.—Technique: Specimens taken during performance of punch biopsy were fixed in formalin and embedded in paraffin. Care was taken to preserve the roof of the bulla when this was present. Various stains were used, including hematoxylin and eosin, Van Gieson's, Masson's trichrome, toluidine blue, Wright's, and Hotchkiss-McManus'.

Results: Biopsies of spontaneous bullae showed that acantholysis was present in all cases of pemphigus vulgaris, pemphigus vegetans, and pemphigus foliaceus. In the lesions in these cases, the acantholytic cell, particularly the nucleus, was undergoing degenerative changes, such as nuclear irregularity and vacuolization. The lesions in cases of familial benign chronic pemphigus showed acantholysis of a different type. In this condition, the acantholytic cells had a regular nucleus and often showed evidence of mitotic figures; also, some cells showed partial retention of their prickles. Biopsies in the two cases in which burns were present showed extensive necrosis of epidermal cells. An increase was noted in the number of endothelial cells and fibroblasts in the cutis.

The lesions in the remaining cases did not show acantholysis.

Biopsy Touch Smears.—Biopsy touch smears in cases of bullous dermatoses had not been done prior to this study, as far as could be ascertained.

Technique: The specimen taken for biopsy was rolled lightly on a dry sponge; the side nearest to the bulla was smeared on four to six slides, and the preparation was stained immediately. Wright's stain followed by counterstaining according to Giemsa's method was found to be satisfactory.

Results: Tzanck cells were found (Fig. 1*c*) in 5 of 13 cases of pemphigus vulgaris.

STUDIES OF ARTIFICIAL BULLAE

Artificial Bullae in the Rabbit's Eye.—Studies were conducted on the nictitating membranes and the tarsal and bulbar conjunctivae of healthy rabbits. Cantharides cerate N.F. was applied to these regions while the animal was under anesthesia induced by means of pentobarbital (Nembutal) sodium. Reactions were observed continuously under the dissecting microscope for three, five, seven, six, and four hours, respectively.

Results: The first change noted was a diffuse brilliant-red hyperemia beneath and around the irritant; later, this hyperemia became severer. The irritant was removed after 1 hour in the first experiment, after ½ hour in the second, and after 20 minutes in the remainder of the experiments. It was noted that hyperemia increased during the half-hour after removal of the cantharides, after which it started to subside. The vessels appeared to be twice their original size, and they became tortuous. Later, the flow of blood in these vessels became slower and slower until it stopped in a tortuosity. A thin blockage was thus formed, and more cells adhered to this as time went by. About the third hour, fluid could be seen traversing the walls of the vessels into extravascular spaces.

Similar results were obtained in a rabbit which received 200 units of heparin intravenously and 150 mg. of bishydroxycoumarin (Dicumarol) by mouth.

Artificial Bullae in Patients Who Had Pemphigus Vulgaris.—Review of the literature revealed that artificial bullae have been employed for therapy, prophylaxis, diagnosis, and determination of the chemical status of the body fluids in systemic and cutaneous diseases.

Many workers have studied the chemical components of the artificial bullae and correlated them with chemical findings in the blood. Some have recovered bacteria from such bullae that were specific to the disease from which the patient was suffering; a few have studied their cytologic features and fewer still their histologic characteristics.

Artificial bullae produced by the application of cantharides have been studied in volunteers who had the following conditions: pemphigus vulgaris (12), suspected pemphigus (8), pemphigus vegetans (1), pemphigus erythematodes (1), suspected pemphigus erythematodes (1), indeterminate oral lesions (6), indeterminate oral and vulvar lesions (3), dermatitis herpetiformis (14), bullous erythema multiforme (6), bullous lichen planus (2), bullous systemic lupus erythematosus (2), bullous lymphoblastoma (1), herpes generalisatus (1), vaccinia (1), chronic porphyria (1), ichthyosiform erythroderma (1), epidermolysis bullosa (1), dermatitis medicamentosa (1), contact dermatitis (2), dyshidrosis (2), tinea pedis (2), acute systemic lupus erythematosus (6), chronic discoid lupus erythematosus (7), dermatomyositis (2), sarcoidosis (1), generalized neurodermatitis (3), and blastomycosis (1). Bullae produced in six apparently normal volunteers also were studied.

The foregoing list includes a total of 95 persons and represents most of the patients in whom spontaneous bullae were studied. In many instances, more than 1 artificial bulla was induced in the same person, the total number of artificial bullae being 131. Smears of the contents of the bullae and scrapings from their floors were made in all instances.

Biopsies of these artificial bullae were made for all patients except those who had the following diseases: pemphigus erythematodes (1), bullous erythema multiforme (2), bullous lichen planus (1), and bullous systemic lupus erythematosus (1). The totai number of specimens removed for biopsy was 124.

Technique: A standard amount of cantharides cerate N.F., measuring about 4 by 4 by 2 mm., was placed on the sterile gauze of an elastic bandage (Band-Aid) and applied to apparently normal skin, preferably on the thigh, where it was kept for a variable length of time, ranging from 10 minutes to 6 hours. The material was then removed, and the surface was cleansed with a small amount of alcohol; a plastic cup was used for protection of the test site after removal of the irritant. This entire procedure is referred to as a "cantharides test." Unless otherwise stated, the cantharides cerate was applied for six hours. The total time of the test was measured from the time at which the cantharides cerate was applied. Thus, a 12-hour cantharides test was one in which the lesion was allowed to develop for six hours after removal of the cantharides. Smears from the contents of the artificial

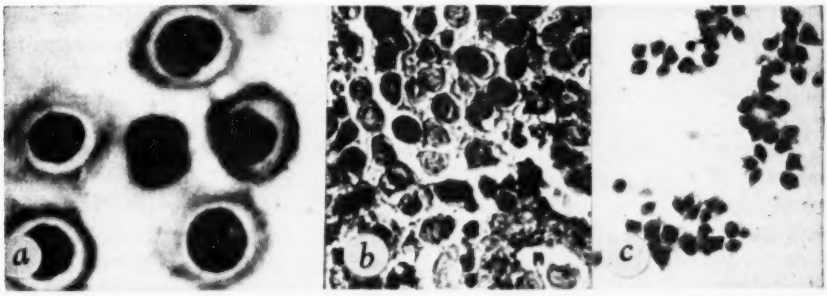

Fig. 2.—(*a*) Smear from a 12-hour cantharides bulla of pemphigus vulgaris, showing five acantholytic cells, each with enlarged and irregular nucleus, numerous nucleoli and vacuoles, and homogeneous cytoplasm. Note dark condensation in form of areola at periphery of acantholytic cells and compare size with that of plasma cell in center. (Wright counterstained with Giemsa; × 875.) (*b*) Section from a gelatinous mass in a 24-hour cantharides bulla of pemphigus vulgaris. Note large number of acantholytic cells and severe necrosis. (Hematoxylin and eosin; × 300.) (*c*) Scrapings from a 12-hour artificial bulla of pemphigus vulgaris, showing acantholytic cells as well as prickle cells that have partially maintained their prickles. (Hematoxylin and eosin; × 150.)

bullae, scrapings from their floors, biopsy specimens, and biopsy touch smears were made and studied in the same way as in the investigation of spontaneous bullae.

Results: Smears taken from a bulla produced by a cantharides test of 12 hours' duration in a case of pemphigus vulgaris showed numerous isolated (Fig. 2*a*) and clumped acantholytic cells. The same change was seen, but to a much less degree, in 20% of the 12-hour cantharides lesions in normal persons and in patients who did not have pemphigus vulgaris. A 24-hour artificial bulla produced in one case in which pemphigus vulgaris was present contained a solid yellowish gelatinous mass; histologic section of this mass disclosed that it was composed of acantholytic cells and amorphous material (Fig 2*b*).

Scrapings from a bulla produced by a 12-hour cantharides test in a case of pemphigus vulgaris showed the presence of acantholytic cells (Fig.2*c*). Findings were similar in 25% of the control lesions induced in normal persons and in those who did not have pemphigus vulgaris.

Cantharides cerate was applied for a period of five hours on various sites in a number of persons, including patients who had pemphigus vulgaris, patients who had miscellaneous dermatoses, and normal persons. The time of appearance of each bulla was recorded, and smears of its contents and scrapings from its floor were made as soon as the lesion appeared; biopsy specimens and biopsy touch smears also were taken at this time.

Biopsies: The first 23 specimens for biopsy were taken with the aid of infiltration with procaine hydrochloride; the remaining 108 were taken without local anesthesia. The tissue was fixed in formalin with the exception of 10 specimens that were fixed in Bouin's fluid. Many sections were studied, including many serial sections. Various stains were used, including hematoxylin and eosin, Van Gieson's, Gram's, Wright's, toluidine blue, iron hematoxylin, Masson's trichrome, Best's carmine, methylrosaniline chloride, and Hotchkiss-McManus'.

Results: During the initial part of this investigation, specimens for biopsy were taken from bullae produced by a 24-hour exposure to cantharides. At first it was thought that exposure for this period would produce acantholytic bullae in persons with pemphigus, whereas nonacantholytic bullae would result in persons who did not have pemphigus. It was later found that 25% of the control lesions induced in persons who did not have pemphigus showed acantholysis. Biopsies of the roofs of bullae produced by 24-hour cantharides tests in normal persons revealed acantholysis.

Cantharides cerate was applied for five hours, as previously mentioned, and biopsy of the bulla was done as soon as the lesion appeared. All patients who had pemphigus vulgaris demonstrated acantholysis in these early artificial bullae; other persons did not, with two exceptions, namely, a normal person and a patient who had severe senile dermatitis herpetiformis associated with cardiac failure. The irritant again was applied to the normal person for five hours, and biopsy was done immediately; no acantholysis was noted after this second application.

Cantharides cerate was applied for three hours to one site and for four hours to another site in a patient who had pemphigus vulgaris. Both bullae so produced displayed acantholysis; lesions induced in four persons who did not have pemphigus did not show acantholysis. Cantharides cerate was applied for three hours to five other patients who had pemphigus vulgaris. Biopsy showed acantholysis in all five, whereas five control lesions showed none.

A bulla was induced on my forearm by means of a drop of boiling oil. Biopsy done without anesthesia 20 hours later revealed necrosis of the epidermal cells with tearing off of the hair follicles (Fig. 3*a*).

Cantharides cerate was applied for three hours to the site at which a 24-hour cantharides bulla had been induced a week before in a patient who had bullous erythema multiforme. The 24-hour cantharides bulla had shown absence of acantholysis, while the 3-hour cantharides bulla (Fig. 3*b*) revealed definite acantholysis indistinguishable from that of pemphigus vulgaris.

Cantharides cerate was applied for 3 hours and 15 minutes to a patient who had pemphigus and who had received prolonged therapy with cortisone. Biopsy showed extensive acantholysis. Three-hour and five-hour cantharides tests made on normal persons resulted in essentially no changes in the former and in early stages of intercellular edema in the latter. This result led to time-sequence studies regarding formation of bullae.

Time-Sequence Studies on Formation of Bullae.—The mechanism of formation of bullae resulting from serial application of cantharides cerate to apparently normal skin was studied in normal persons, in patients who had pemphigus vulgaris, and in patients who had other types of bullous dermatoses or miscellaneous cutaneous diseases. Such studies had not been done before, as far as could be determined. Punch biopsies of the test site were done without anesthesia immediately after removal of the irritant and also of other test sites at measured intervals after removal of the irritant. This procedure is referred to as a "cantharides-irritation biopsy."

Thus, cantharides cerate was applied for 10, 30, 50, 70, 90, 105, 120, 140, 160, and 180 minutes to various surfaces of the skin of patients who had pemphigus vulgaris, after which times biopsies were taken without anesthesia. The same procedure was carried out for another group of persons, some of whom apparently were normal, whereas others presented different types of bullous dermatoses or miscellaneous cutaneous diseases. Cantharides cerate was applied for 3 hours to various sites in both groups, and biopsy was done 15, 30, 45, 60, 90, 120, 150, and 180

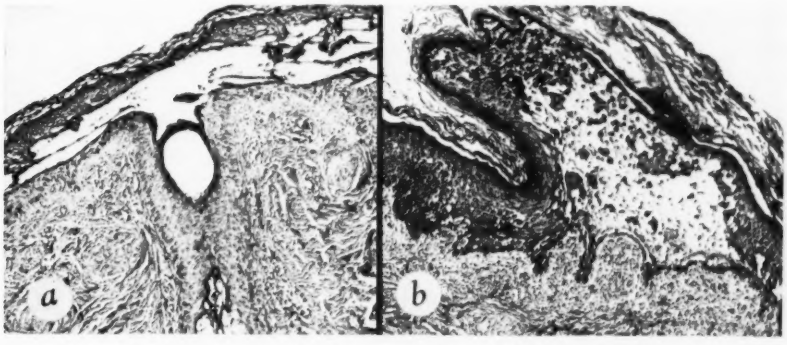

Fig. 3.—(*a*) Twenty-hour bulla induced by drop of boiling oil. Section shows disintegration and necrosis of epidermal cells. Hair follicle is torn off. Floor of bulla is fairly smooth. Cutis shows proliferation of endothelial cells and fibroblasts. (*b*) Histologic appearance after second application of cantharides in patient who had bullous erythema multiforme. (*a* and *b*, hematoxylin and eosin; × 50.)

minutes and then every successive hour up to 21 hours after removal of the cantharides. Biopsies of apparently normal skin were made at the same time for both groups of persons.

Results: It was noted that the initial lesion was in the individual prickle cell in pemphigus vulgaris. A 105-minute cantharides-irritation biopsy of a patient who had pemphigus vulgaris showed increase in size of the prickle cells, which became rounded, diminution in the number of intercellular bridges, and thinning of the remaining bridges. The nuclei were enlarged and showed prominent nucleoli; no change was noted in the cutis (Fig. 4*a*). The next change noted, which was seen in a 120-minute cantharides-irritation biopsy, showed established acantholysis that was complete in one cell and partial in four surrounding prickle cells. The acantholytic cell appeared to be completely devoid of its prickles (Fig. 4*b*). The acantholytic cell itself was spherical, with a dark peripheral areola; the nucleus was enlarged and had numerous prominent nucleoli. The cutis showed no change.

A 140-minute cantharides-irritation biopsy of the same patient showed the formation of two clefts in the deeper layers of the stratum malpighii above the basal layer. The floor of the first cleft was composed of about 10 basal cells adhering to the cutis. These basal cells had a smooth, free surface. Many acantholytic cells were present, of which five or six were completely free (Fig. 4*c*). The floor of the other cleft was composed of about 25 basal cells firmly attached to the cutis. Again,

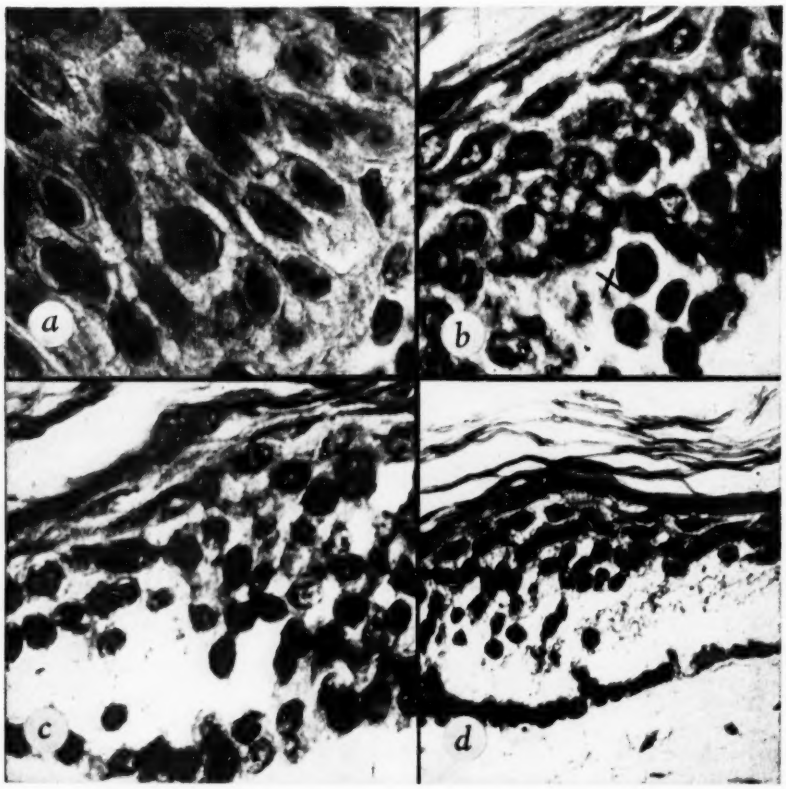

Fig. 4.—(*a*) Section of 105-minute cantharides-irritation biopsy specimen from patient who had pemphigus vulgaris. Prickle cell in middle of field (*X*) is enlarged and spherical; nucleoli are prominent, and prickles are thinned out. (Hematoxylin and eosin; × 1,000.) (*b*) Two-hour cantharides-irritation biopsy specimen from patient who had pemphigus vulgaris. Completely acantholytic cell (*X*) shows extremely large nucleus and prominent nucleoli. An intercellular bridge is possibly present. (Masson trichrome; × 1,000.) (*c*) Section of 140-minute cantharides-irritation biopsy specimen from same patient, showing acantholytic cleft, floor of which is basal layer. (Masson trichrome; × 650.) (*d*) Same as *c*, showing similar but larger cleft. (Masson trichrome; × 450.)

many acantholytic cells were present, many of which were free (Fig. 4*d*). The cutis showed a moderate degree of inflammation.

A 160-minute cantharides-irritation biopsy of another patient who had pemphigus vulgaris disclosed an acantholytic bulla with a ragged contour and angulated margins. The floor was formed of basal cells sticking up into the cavity of the bulla:

the roof also was irregular, rounded, and apparently under tension. Many acantholytic cells were present, some free and some still attached to other acantholytic cells (Fig. 5*a*). Examination by means of higher magnification showed the presence of isolated and grouped acantholytic cells; the basal-cell layer formed the floor of the cleft. The cutis showed a mild degree of inflammation; the vessels were slightly dilated and the papillae had a wavy appearance (Fig. 5*b*). An early spontaneous

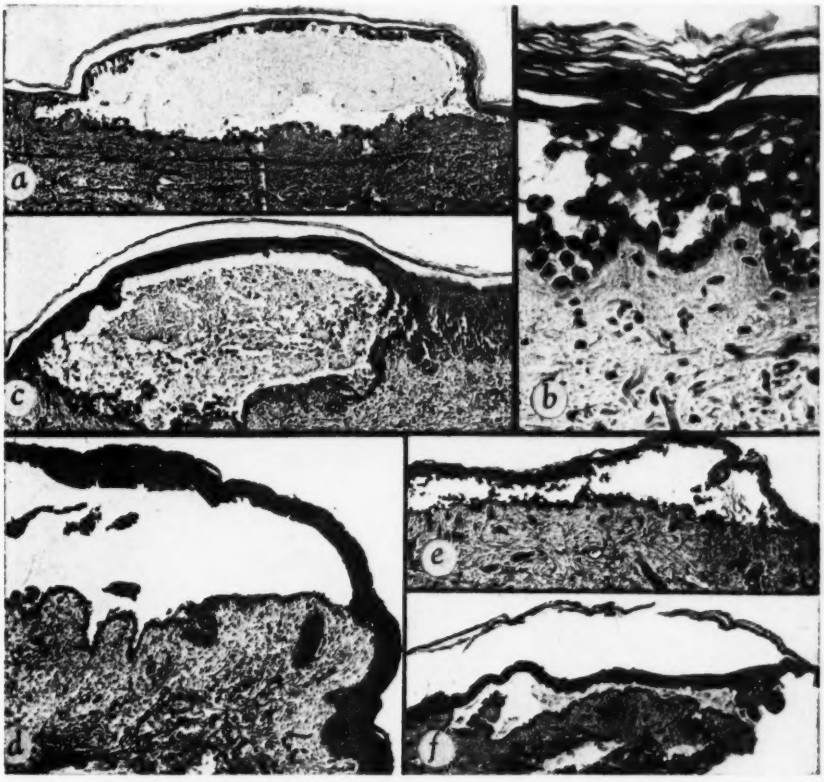

Fig. 5.—(*a*) Section of 160-minute cantharides-irritation biopsy specimen from patient who had pemphigus vulgaris, showing acantholytic bulla with ragged contour; angulated margins are indistinguishable from those of early spontaneous bulla in patient represented in *c*. (Hematoxylin and eosin; × 40.) (*b*) Higher magnification of cleft seen at extreme left of *a*, showing wavy appearance of floor formed by basal cells. Many acantholytic cells are present. (Masson trichrome; × 275.) (*c*) Early spontaneous bulla in same patient; compare with that shown in *a*. (Hematoxylin and eosin; × 50.) (*d*) Appearance of 180-minute cantharides-irritation biopsy specimen from patient who had pemphigus vulgaris, showing crypts in floor of bulla and clusters of acantholytic cells. (Masson trichrome; × 60.) (*e*) Section of 195-minute cantharides-irritation biopsy specimen from same patient, showing tearing off of hair follicle in highly acantholytic bulla. (Masson trichrome; × 55.) (*f*) Spontaneous early bulla in same patient. (Masson trichrome; × 30.)

bulla in the same patient (Fig. 5*c*) was histologically almost indistinguishable from the artificial bulla (Fig. 5*a*).

A 180-minute cantharides-irritation biopsy of another patient who had pemphigus vulgaris showed a large bulla with a serrated floor formed of basal cells adhering

to the cutis and projecting out into the cavity of the bulla, in which acantholytic cells could be seen. Proliferation of the papillae was intense, and the floor of the bulla had the appearance of being indented by numerous crypts (Fig. 5*d*). A 195-minute cantharides-irritation biopsy of the same patient showed breaking off of the

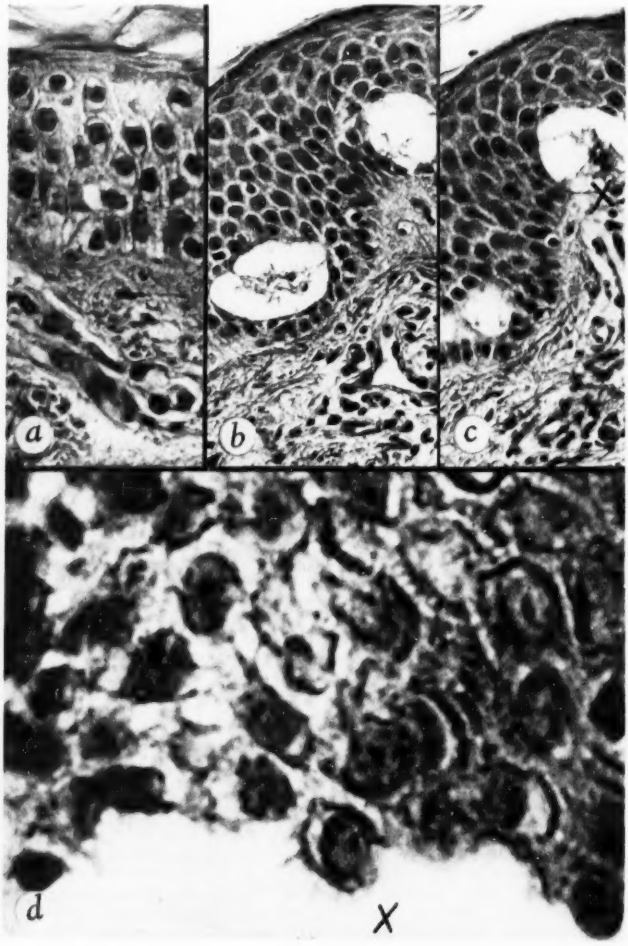

Fig. 6.—(*a*) Section from five-hour cantharides-irritation biopsy specimen from patient who had exfoliative dermatitis. Note dilatation of papillary vessels, elongation of intercellular bridges, and beginning intercellular edema (hematoxylin and eosin; × 500.) (*b*) Appearance after seven-hour cantharides test in patient who had epidermolysis bullosa. Note formation of two vesicles, one among prickle cells and one located subepidermally. (*c*) Serial sections of same lesion, showing almost direct communication between papillary vessel and subepidermal vesicle. They are separated only by wall of vessel. Leucocyte at *X* is seen in ameboid movement traversing wall of vessel into cavity. (*b* and *c*, hematoxylin and eosin; × 250.) (*d*) desmorhexis in section obtained after 20-hour cantharides test from patient who had severe dermatitis herpetiformis. In center of field (*X*) facing cavity is perfectly normal prickle cell with normal but ruptured intercellular bridges. (Hematoxylin and eosin; × 1,200.)

hair follicles (Fig. 5*e*), in addition to the changes just described. An early spontaneous bulla from the same patient disclosed essentially the same phenomena (Fig. 5*f*).

The changes thereafter varied considerably; more acantholysis occurred, and eventually few or no epidermal cells were left.

The histologic changes after application of cantharides cerate to patients who did not have pemphigus vulgaris differed considerably in time as to the onset and

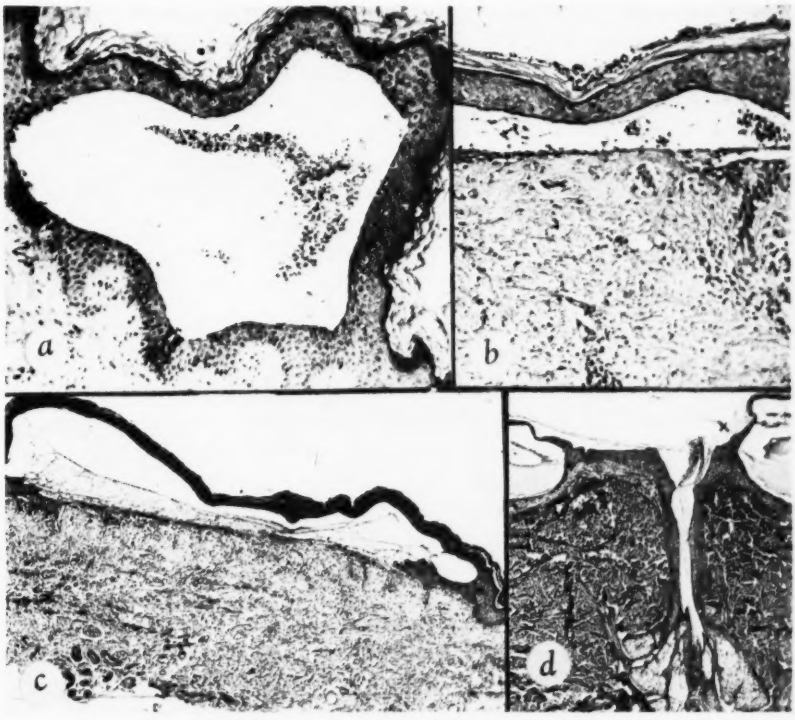

Fig. 7.—(*a*) Section obtained after 16-hour cantharides test from patient who had bullous erythema multiforme, showing intraepidermal location of bulla. No acantholysis is present, and margins are smooth. Roof of bulla is under pressure. (Masson trichrome; × 125.) (*b*) Section obtained after 17-hour cantharides test from patient who had dermatitis herpetiformis. Note large subepidermal bulla. Epidermal cells are intact. Roof is collapsed, being no longer under pressure. (Hematoxylin and eosin; × 125.) (*c*) Spontaneous bulla in patient who had dermatitis herpetiformis. Floor is subepidermal, but margins are intraepidermal. (*d*) Section obtained after 24-hour cantharides test from patient who had lichen planus; note bulla at each side of hair follicle. Bulla advanced by progressing along hair follicle at *X*. (*c* and *d* hematoxylin and eosin; × 30.)

sequence of events. They also varied from one person to another, as well as in the same person. However, the pathologic physiology of formation of bullae in patients who did not have pemphigus vulgaris was essentially the same.

The first change noted in patients who did not have pemphigus vulgaris was in the vessels of the upper part of the cutis, manifested by dilatation of the papillary vessels; this was followed by elongation of the intercellular bridges and beginning

edema between the cells of the deeper layers of the epidermis (Fig. 6*a*). These changes were noted first in the 160-minute cantharides-irritation biopsy and were still present in some cases in the five-hour specimen.

The next change was a moderate degree of perivascular infiltration, with formation of one or more tiny vesicles within the epidermis or at the epidermodermal junction (Fig. 6*b*). Serial sections of the lesion pictured in this figure showed almost direct communication between the papillary vessel and the vesicle on the right, the only separation being the wall of the vessel. A leucocyte was seen in an ameboid movement traversing the wall of this vessel into the cavity of the bulla (Fig. 6*c*). The vesicles enlarged and if close enough finally coalesced.

The pressure in the vesicles increased, the intercellular bridges bearing the brunt of this force. At first they resisted and elongated, but then they broke off, a process that I should like to refer to as "desmorhexis" (Fig. 6*d*).

The vesicle increased in size as serum and leucocytes from the papillary vessels flowed into it (Fig. 7*a*). Generally in conditions other than pemphigus vulgaris, when the lesion starts as an intraepidermal vesicle, it becomes an intraepidermal bulla (Fig. 7*a*); if it starts as a subepidermal vesicle, the bulla will be subepidermal (Fig. 7*b*); if two vesicles are present, one within and one below the epidermis (Fig. 6*b* and *c*), and if they coalesce, then the floor of the bulla will be partially subepidermal and partially intraepidermal. Figure 7*c* shows a spontaneous bulla of dermatitis herpetiformis for comparison; this displays intraepidermal margins at both ends and a subepidermal floor. Sometimes study of serial sections of a lesion that appeared to be a subepidermal bulla disclosed that it was intraepidermal in part of its extent; the opposite was also true.

During a 24-hour cantharides test on a patient who had lichen planus, two bullae developed, one on each side of a hair follicle. The bullae progressed around the hair follicle (Fig. 7*d*) but did not break it off, as in the case of the 195-minute cantharides-irritation biopsy (Fig. 5*e*) of a patient who had pemphigus vulgaris

SUMMARY AND CONCLUSIONS

Smears from the contents of bullae, scrapings from their floors, specimens removed for biopsy, and biopsy touch smears from 92 patients who exhibited various types of bullous dermatoses were studied. In addition, studies were made of artificial bullae produced by application of cantharides cerate N.F. to the eyes of rabbits, to the skin of 89 volunteers who had various types of bullous dermatoses, and to the skin of 6 normal volunteers.

Smears of contents of bullae and scrapings from their floors showed Tzanck cells in all 13 cases of pemphigus vulgaris and in one case each of phemphigus vegetans and pemphigus foliaceus. Scrapings in three cases of familial benign chronic pemphigus were specific, in that they showed the presence of acantholytic cells, some of which were undergoing mitotic division; a few prickle cells retained part of their prickles.

Smears from the contents of bullae and from scrapings in the remaining cases of bullous dermatoses were nonspecific and not diagnostic.

The Tzanck cell was found in biopsy touch smears in 5 of 13 cases of pemphigus vulgaris.

The term "acanthorhexis" is proposed to denote the presence in scrapings of normal isolated prickle cells, still bearing their prickles. These cells have been scraped off forcibly during the procedure.

Acantholysis was the primary change caused by application of cantharides to apparently normal skin of patients who had pemphigus vulgaris; pressure phenomena were secondary. The only persons who displayed acantholysis in three-hour cantharides-irritation biopsies of apparently normal skin were those who had pemphigus vulgaris. Thus, the optimal time for study of the cantharides-irritation biopsy specimen was at three hours.

Occurrence of acantholysis in the cantharides test of persons who did not have pemphigus vulgaris was a secondary phenomenon, as shown by its absence in the early cantharides-irritation biopsies in this group. Cantharides applied to already damaged skin, such as that which had been the site of a recent bulla produced by cantharides, brought about acantholysis early in the process.

The pathologic physiology of formation of bullae was demonstrated in patients who had pemphigus vulgaris by means of biopsies done after serial applications of cantharides to apparently normal skin. A comparison was made with similar studies of normal persons and of patients exhibiting miscellaneous dermatoses other than pemphigus vulgaris. The early changes in pemphigus vulgaris were in the prickle cell itself, with lysis of the intercellular bridges (acantholysis) leading to an intra-epidermal cleft and consequent formation of bullae. In the miscellaneous group of persons, the early changes consisted in dilatation of papillary vessels, with consequent flow of fluid through the walls of the vessels; this caused pressure on the junction between epidermis and cutis or between the prickle cells, with separation of the epidermis from the cutis or rupture of the intercellular bridges and consequent formation of bullae.

The term "desmorhexis" is proposed to indicate the forceful rupture of intercellular bridges caused by mechanical pressure (flow of fluid) acting on them. Desmorhexis is the method by which bullae are formed in dermatitis herpetiformis, bullous erythema multiforme, bullous lymphoblastoma, bullous lupus erythematosus, bullous lichen planus, and epidermolysis bullosa. This change is opposed to acantholysis, which is a disease process of the intercellular bridges themselves and which is the primary lesion in the bullae of pemphigus vulgaris.

This problem merits further investigation.

ABSTRACT OF DICUSSION

DR. H. E. MICHELSON, Minneapolis: First I must commend Dr. Brennan for his industry and for his fine work in verifying Civatte's and Tzanck's observations on bullous eruptions, and congratulate him for his original investigations. His work tends to justify the contention of the French and of other students of pemphigus that histologic findings are of diagnostic value and, in fact, are conclusive in making a diagnosis of pemphigus vulgaris.

The histology of bullae had been studied by all dermatopathologists for a long while, but the location of the blister, i. e., the plane in which it existed, attracted more attention than the cytology of the separated cells. Civatte, Tzanck, and their pupils have continued their studies and have concluded that one who is familiar with their criteria may faithfully and with certainty differentiate pemphigus vulgaris from the other bullous eruptions.

One who has microscopically examined bullae from many patients for whom the diagnosis of pemphigus vulgaris has been made is struck by the fact that clinical pemphigus vulgaris often does not have microscopic verification. What then is the diagnosis? To the French the condition would be called dermatitis herpetiformis. In this country most of us, at any rate I, have strict

criteria for the diagnosis of dermatitis herpetiformis, which include polymorphy, characteristic topography, severe subjective symptoms, and chronicity. Purely bullous dermatitis herpetiformis in adults is a rarity. What, then, is the diagnosis of a bullous eruption which morphologically is pemphigus but histologically is not? What course is to be expected? What response to treatment is to be expected? What is the prognosis? I do not believe we can answer these questions with complete certainty as yet. We can say, however, that most patients with severe pemphigus vulgaris do show the acantholysis of Civatte and the cells of Tzanck.

The admirable work of Dr. Brennan, assisted by Dr. Montgomery, has led us a long way toward perfection in the diagnosis of pemphigus vulgaris. The follow-up of patients, the results of treatment, and the eventual outcome when tabulated will undoubtedly result in most useful and practical formulae for evaluating bullous diseases.

The Association should feel deeply indebted to Dr. Brennan, and the committee made a delightful choice when they made it possible for this essay to be presented at this meeting.

DR. FRANCIS W. LYNCH, St. Paul: I thoroughly enjoyed the opportunity to read Dr. Brennans' essay, and I wish to add my congratulations. A few brief comments may emphasize the nature of the work described in his paper. Dr. Brennan has studied bullous diseases by means of smears, scrapings and biopsy specimens and has added a technique, that of biopsy touch smears. In his experiments he found the smears not to be completely dependable, with repeated studies necessary in 25% of the cases of pemphigus. Scrapings proved possibly not dependable in at least two cases of oral lesions. With touch smears his results were interesting but not completely dependable. The best diagnostic results were noted with biopsy, although acantholysis was also observed in benign pemphigus of Hailey and Hailey. These phases of Dr. Brennan's work are very worth while, but his major contribution has been the survey of bullae produced artificially in animals, persons without pemphigus, and patients with pemphigus. At certain stages in the development of such blisters in the absence of pemphigus, he noted acantholytic cells, apparently not distinguishable from those of pemphigus.

Dr. Brennan went on to show that the essential difference is in the mechanism of development of the various types of blisters and that in studying the blister of pemphigus there is an optimal time. At least in pemphigus the characteristics of the blister thus depend not only on the site of the blister or the presence or absence of acantholysis, but on pathogenesis, the manner in which the blister has developed. Dr. Brennan certainly deserves our sincere congratulations for his extensive investigations and his very worth-while contributions.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: It has been a pleasure to follow Dr. Brennan's work on this subject during the past several years. His tradition of multilanguage background and his knowledge of European workers, especially those in Paris, on this particular subject were a great stimulation and help to him.

In the first place, Dr. Brennan reviewed the records of patients with bullous dermatoses in the files of the Mayo Clinic. In studying the biopsy specimens of such patients and referring to the clinical records and follow-up data, he was able to establish a high correlation between the presence of acantholysis in those long-dormant biopsy specimens and the clinical course of the patient.

It was recognized early that biopsy specimens of bullae from patients with pemphigus showed inconsistent results, owing to the fact that there was no standard way to estimate the life of the bullae. With this fact in mind, Dr. Brennan utilized a procedure in which a standard cantharide vesicant was applied to the uninvolved skin of such patients for varying periods and the histologic picture of the bullae produced was then studied in time sequence. He found that the specimen obtained three hours after the cantharides had been applied provided the optimal histologic opportunities.

DR. FRANCIS A. ELLIS, Baltimore: I have enjoyed this paper very much. I had previously seen Dr. Brennan's work, and I fully agree with his conclusions and, like Dr. Lever and others, have come to the belief that one should not diagnose pemphigus vulgaris acutus without the confirmation of a biopsy. It is true that one must get the biopsy specimen at the proper stage. Dr. Ketron reviewed some of our material, and we practically arrived at this conclusion: Bullae that did not show the typical biopsy picture were not lesions of pemphigus acutus. This finding is very important, because in many reports on the treatment of pemphigus the data do not

make certain that the patient had pemphigus vulgaris acutus. Dermatologists all have difficulty diagnosing the bullous eruptions of older patients, and a series of reports on therapy may be misleading because they have not included only cases of pemphigus.

Of course, we have had an interest in so-called "Hailey and Hailey benign pemphigus," which we are not at present willing to accept as being a form of pemphigus. I should like to ask Dr. Brennan again whether he found any difference between acantholytic cell in this disease and in pemphigus acutus. Dr. Winer also did some work along this line, and he may want to say a word about his findings.

Dr. Louis H. Winer, Beverly Hills, Calif.: I wish to congratulate the essayist on a brilliant piece of work. He used a scientific procedure to produce artificially something which had been occurring naturally in his patients. Examining the resultant lesions by numerous methods, he was able to find the cells typical of the diseases. He also found a characteristic rupture of the follicle in pemphigus which was not duplicated in other diseases.

To be adept in cytology of the skin, one must make repeated studies, even though one is doing histopathology. On the other hand, one cannot render opinions on cells unless a histologic section is studied simultaneously with the cytologic smear. I say this for the reason that cells from different areas and scrapings from different areas vary. For instance, scrapings from the buccal mucosa differ from scrapings from the lingual mucous membrane because of differences in epithelium.

As important as knowledge of the site of the scrapings is the magnification used to examine the slide. If one looks at the smears under 120 magnification, one will find that cells of pemphigus, bullous urticaria pigmentosa, and other epitheliolytic processes all appear to be the same. But if one examines these smears under higher magnification, say at 320 or even higher, one is able to see the characteristic changes which occur in the cytoplasm, such as condensation at the border of the pemphigus Tzanck cell, as well as the epitheliolytic phenomena. There are several loopholes for confusion to enter this field of investigation.

Dr. Howard Hailey, Atlanta: In one of my reports, I pointed out that one can produce an extension of lesions of familial benign chronic pemphigus with the use of ultraviolet light. I should like to suggest that if Dr. Brennan continues his investigation he use ultraviolet light (either the Kromayer light or the open air-cooled light) and try to determine whether there is any difference in the cellular response to the physical agent, as compared with the chemical agent.

Dr. Frank C. Combes, New York: I, too, have enjoyed Dr. Brennan's article immensely. I think the most important thing, the basis for all the reasoning, is the artificial production of a blister. Much of the confusion in the histological diagnosis of pemphigus has been due to variations in the time and site at which the biopsy specimen was taken, whether the center of the blister or the progressing edge was taken.

In his concluding remarks, I wish Dr. Brennan would state the site at which he prefers to produce the blister. In some work on the McClure-Aldrich test many years ago, I observed that the cutaneous absorption of the injected saline was much more rapid on the thigh than it was on the forearm; if the absorption of this fluid is due to desmorhexis, as Dr. Brennan has suggested, one can appreciate the importance of the site at which he raises the blister.

Dr. Joseph G. Brennan, Rochester, Minn.: I wish to thank the discussers. A standard amount of cantharides cerate was applied to the apparently normal skin of human volunteers. Various sites were tested, but the thigh was preferred. Biopsy specimens were taken without anesthesia. It was thought at first that a 24-hour cantharides-irritation biopsy specimen showed histologic changes that were specific for pemphigus vulgaris, but it was found later that the changes were inconsistent.

Cantharides was then applied to various parts of the skin of various persons, and biopsy specimens were taken at selected intervals thereafter. This procedure led to time-sequence studies. It was noted that in cases of pemphigus vulgaris changes could be seen even in the 105-minute cantharides-irritation biopsy specimens. This finding was not noted in the control cases.

In regard to the phenomenon of acantholysis, it is emphasized that loss of intercellular bridges can take place in many conditions. It may be seen in benign and malignant dyskeratoses, in cutaneous disorders of viral etiology, and in chronic benign pemphigus. The acantholytic cell in

the last-named condition shows evidence of multiplication by mitotic and amitotic division. in pemphigus vulgaris the acantholytic cell shows evidence of death. This subject is taken up in another paper.[1]

I wonder whether I have answered all the questions?

DR. LOUIS A. BRUNSTING, Rochester, Minn.: How long is the cantharides left on the skin?

DR. JOSEPH G. BRENNAN: Cantharides was left on the skin for periods ranging from 10 minutes to 6 hours. The optimum time for study, however, was found to be three hours.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: How long after cantharides is removed is the biopsy specimen taken?

DR. JOSEPH G. BRENNAN: Biopsy specimens were taken immediately after as well as at various intervals after removal of cantharides.

DR. HOWARD HAILEY, Atlanta: Did you have occasion to study the cells from bullous urticaria?

DR. JOSEPH G. BRENNAN: Acantholysis was not present in sections from the patients with bullous urticaria who were studied.

The possibility of producing bullae by means of ultraviolet radiation was investigated. Meladinin (a preparation containing ammoidin and ammidin) was applied to apparently normal skin; the area was then treated with ultraviolet rays. The results were not satisfactory.

Bullae were also produced on human volunteers by means of boiling oil; necrosis of the epidermal cells was present histologically.

QUESTION: Did bullae produced by pinching show the same phenomena?

DR. JOSEPH G. BRENNAN: The Nikolsky phenomenon was studied. I do not think very highly of it. This phenomenon was produced inconsistently in cases of pemphigus vulgaris. It was also possible to produce it sometimes in normal infants and in cases of dermatitis herpetiformis. It was studied histologically. It is not reliable.

QUESTION: Did you try to produce bullae in the mucous membrane of the mouth?

DR. JOSEPH G. BRENNAN: Yes, in animals and by various methods, with cantharides, and with submucosal injection of a solution of 10% urea. Cats were used at first, but they have small mouths, and dogs were therefore preferred. There was no acantholysis in the early bullae studied.

PSYCHOSOMATIC DERMATOLOGY CIRCA 1850

SAMUEL D. ALLISON, M.D.
HONOLULU, T. H.

EMOTIONS produced disease before the present interest in psychosomatic medicine. This statement may seem trite, but many people forget that the role of emotion in disease was well recognized by physicians long before the appearance of the present spate of papers on the subject. Certainly, the present interest in psychosomatic medicine is laudatory, but we should not forget that physicians throughout the ages have been very much concerned with this aspect of medicine.

In order to see what was being written concerning the emotions and their role in diseases of the skin, I recently reviewed Erasmus Wilson's two volumes of a century ago. The first of these, "Diseases of the Skin" [1] is a 650-page text regarded as the standard work in dermatology of its day. The second, "The Skin and Hair," [2] was a short popular treatise on the subject. These volumes are replete with references to the role of emotions in skin disease and, interestingly enough, the observations coincide quite closely with the popular accepted ideas of today. For example, there is today quite general agreement that certain conditions such as delusions of parasitosis and syphilophobia are purely of emotional origin. Wilson [3] describes beautifully delusions of parasitosis as follows:

> In a previous chapter . . . I have mentioned as disorders of sensation, the feelings of tingling, smarting, pricking, shooting, creeping, tickling, burning, scalding, etc. A singular example of one of these sensations, namely, creeping, has several times come before me. I have been consulted by patients, for the destruction of living creatures with which they conceive themselves infested. They have never seen any insect, they have only felt them running along their bodies. A young lady, a governess, who suffered in this way, was in the most distressing state of mind; she had changed her lodgings time after time but the insects ever went with her, and she was afraid of going near the children it was her business to instruct, lest she might communicate her malady to them. I pressed her as to her having seen any of the creatures; she said she had; I then requested her to bring me one or more, if she could catch them, that I might examine them; she was long before she returned, and when she did, she brought three small specimens of a small, harmless insect, commonly found in the crevices of old wood. She had caught them on her bedroom table. For herself, a cleaner or purer being could not exist; and I had the satisfaction of receiving her thanks for being cured, some weeks afterwards. Then I saw, in consultation a gentleman who believed his head peopled with an insect multitude; he could feel them running hither and thither; he could see his hair moved by them, but he had never discovered an animal of any sort, nor could any one else. A gentleman, one day sitting before me with his chest bared, exclaimed: "There, I feel one running across my breast now." I looked, there was nothing to be

1. Wilson, E.: On Diseases of the Skin, Ed. 4 (American), Philadelphia, Blanchard & Lea, 1857.

2. Wilson, E.: Healthy Skin: A Popular Treatise on the Skin and Hair, Their Preservation and Management, Ed. 2 (American), Philadelphia, Blanchard & Lea, 1854.

3. Wilson,[2] pp. 242-244.

seen; it was a visionless ghost; no small annoyance, however, to be haunted by such ghosts. On more than one occasion, I observed that the direction of the creeping or running sensation corresponded with that of the distribution of the nerves, which were the real cause, the feeling being a ghostly sensation. Very commonly, the sensation affected the hairs of the limbs, and seemed to give a preference to those organs as their seat of manifestation. A young gentleman, educating for the church and who had been a great sufferer from this discomfort, came to me, saying that he was much better, so far as the insects were concerned, but that he suffered now from a deeper sensation of motion, in a word, from the feeling of the normal movement of the bowels, the persistaltic motion, as it is called. Now, happily, we are so constituted that, in a state of health, we have no sensation of the internal movements of the body, as of the heart, the lungs, the stomach, the alimentary canal, the muscles; or of the motions of the blood in its vessels. Whenever, from unhealthy action, we are made aware of such motion, the condition is one of disease; being either a diseased condition of the parts which create the sensation, or an over-sensitive and, consequently, a disordered state of the nerves and nervous system. The latter was the case in the last-named gentleman; he said of himself, that he felt unhinged, unfit for his profession, unfit for everything; he was restless, unsettled, unable to remain in a place for any time, and unable even to sit still. In such a person, we should not be surprised to find unnatural and morbid states of sensation, such as creeping, nor that those feelings should degenerate in time into sensations of a more painful character.

While there is general agreement that maladies such as described above are purely related to the emotions there are other conditions such as urticaria and the neurodermatitis group in which there is considerable difference of opinion as to the relative role of emotions, allergans, and other factors. Sulzberger [4] recently excluded all forms of eczema, lichen chronicus simplex (localized), urticaria (other than cholinergic), and atopic dermatitis from a list of conditions in which he believed emotions played a "prompt, major, and indubitable" effect. On the other hand, Alvarez [5] has been very enthusiastic about the role of emotions in urticaria. A number of people have discussed emotion as a factor in the neurodermatitis group, and, recently, Williams [6] has depicted the undeniable part played by emotions in infantile eczema. When maternal rejection was managed, as well as customary treatment given, there were distinctly more babies free from dermatitis at the end of the observation period than among those babies handled in the customary fashion. Copious quantities of kind, tender, and loving mother care paid off. Recently, the work of Guy [7] gives rather conclusive evidence that there are neurogenic factors in contact dermatitis. With use of a "tension box" to disturb known reactive laboratory animals distinctly greater reactions were noted to patch tests following stress than under normal testing conditions. In spite of the reluctance of some people to accept the "prompt, major, and indubitable" effect of emotions on the above-mentioned conditions, most of us have observed urticaria and neurodermatitis either caused by or intensely aggravated by emotional problems of one sort or another.

4. Sulzberger, M. B., and Baer, R. L.: The 1951 Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1952, p. 35.

5. Alvarez, W. C.: The Neuroses: Diagnosis and Management of Functional Disorders and Minor Psychoses, Philadelphia, W. B. Saunders Company, 1951, pp. 444 and 467.

6. Williams, D. H.: Management of Atopic Dermatitis in Children: Control of the Maternal Rejection Factor, A. M. A. Arch. Dermat. & Syph. **63**:545-560 (May) 1951.

7. Guy, W. B.: Neurogenic Factors in Contact Dermatitis, A. M. A. Arch. Dermat. & Syph. **66**:1-8 (July) 1952.

Many of these same relations were recognized by Wilson.[8] He wrote:

Among the causes of urticaria, nervous debility, occasioning a peculiar susceptibility of the cutaneous nerves, must not be omitted. In a lady who was lately under my care, I have watched the red wheals appear and creep along the skin and disappear, while I purposely engaged her in conversation on indifferent subjects. A word, a look, the slightest excitement, would immediately bring out a copious eruption.

I recently had an interesting case of a 14-year-old boy who was involved in his first major love and in whom hives developed every time he called his girl friend.

Wilson[9] also attributed emotions as one of the causes of lichen urticatus. "The pimples . . . are also excited by mental emotion thus, if she be scolded, the itching begins; and, to use her mother's expression, she can at all times 'rub them up wherever she likes.'" Similarly, prurigo mitis[10] "is brought on by mental emotion. . . ." Wilson's[11] remark is also interesting in reference to pruritus vulvae.

Prurigo Pudendalis is a most distressing affection, but, happily, one of unfrequent occurrence. The disease is situated chiefly on the labia majora, and mucous membrane of the vulva, but sometimes extends upwards along the vagina. The pruritis is generally constant, and so violent as to induce an unceasing necessity for friction with hard substances, or scratching. The continuance of the itching produces inflammation and swelling of the parts affected, and induces symptoms approaching to nymphomania.

One of Wilson's statements regarding eczema has been extremely useful in interpreting that picture to patients. As to the cause of eczema, he[12] considers, among other things, "affections of the nervous system, as mental emotions, particularly of the depressing kind." And with regard to prognosis, he[13] states, that "eczema acts very commonly as a safety-valve to the health of the system, and the discharge by which it is accompanied must be checked very guardedly, and not before a counteraction, . . . has been established by art."

From these quotations it is readily apparent that the emotional cause or aggravation of urticaria and the eczematous eruptions was quite well known to our professional pre-Freudian ancestors.

A fascinating phase of dermatology is the study of the common, or vulgar, wart. It is generally recognized that while warts are a virus infection they respond to cures by suggestion. The latter fact has been known for generations. However, it is interesting to note what Wilson had to say about the management of warts. While he discussed the destructive management of them, he also remarked[14] that

a gentleman who takes much pleasure in philosophical pursuits, informs me that he removed an entire crop of warts from his knuckles and fingers by subjecting them to a succession of sparks from one of the poles of an electrical machine. He was in the habit, as is usual, of trying the amount of electric fluid collected in his machine by placing his knuckle near the brass knob, and receiving a spark. Observing that an odd sensation was produced whenever the spark struck a wart, he was tempted for amusement to give them a round of discharges. When his attention was next directed to his hands he found, to his surprise and satisfaction, that all the warts had disappeared. With respect to other modes of treatment, I may say, with Turner [Daniel Turner

8. Wilson,[1] p. 142.
9. Wilson,[1] p. 150.
10. Wilson,[1] p. 160.
11. Wilson,[1] p. 162.
12. Wilson,[1] p. 186.
13. Wilson,[1] p. 187.
14. Wilson,[2] p. 235.

wrote a "Treatise of Diseases Incident to the Skin" in 1714], "I shall not stay to enlarge upon some other remedies, having little other than direct foolery or superstition for their foundation; such as cutting a certain stick with so many notches, the stealing of beef to rub them with, and, after, burying the same in the earth."

Wilson [15] further quoted Mason Good, who observed

that in Sweden, warts are destroyed by the Gryllus verrucivorus, or wart-eating grasshopper, with green wings, spotted with brown. The common people catch it for this purpose; it is said to operate by biting off the excrescence, and discharging a corrosive liquor on the wound.

The major roles of emotion in dermatologic disease have been discussed. The reader may be interested in Wilson's remark as to methods of alleviating itching. Concerning general pruritus, he wrote:[16]

It is interesting to remark the extent to which these painful sufferings are subject to the influence of the nervous system. So long as the mind is engrossed with agreeable occupation, or is diverted from the disorder, the morbid sensation sleeps; but the instant the thoughts are turned to the affection, the pruritus is aroused, and rages with severity. The apprehension of an attack will, in this way, often excite it, and every effort for its relief will but prolong its continuance.

Quoting Hufeland, Wilson stated [17] that

Joy is one of the greatest panaceas of life. No joy is more healthful or better calculated to prolong life than that which is to be found in domestic happiness, in the company of cheerful and good men, and in contemplating with delight the beauties of Nature. A day spent in the country, under a serene sky, amidst a circle of agreeable friends, is certainly a more positive means of prolonging life, than all the vital elixirs in the world. Laughter, that external expression of joy, must not here be omitted. It is the most salutary of all the bodily movements; for it agitates both the body and the soul at the same time, promotes digestion, circulation, and perspiration, and enlivens the vital power in every organ.

Now that the role of emotion in disease has been presented as well as some of Wilson's observations as to the alleviation of disease, there seems to be no more fitting way to draw this paper to a close than to repeat with Wilson [18] the ageless appeal of Macbeth to his physician:

> Canst thou not minister to a mind diseased;
> Pluck from the memory a rooted sorrow;
> Raze out the written troubles of the brain;
> And with some sweet, oblivious antidote,
> Cleanse the full bosom of that perilous stuff
> Which weighs upon the heart?

SUMMARY

There has been presented a review of some of the remarks of Erasmus Wilson, a famous mid-19th century physician and philanthropist, on the emotional origin and alleviation of dermatologic distress. One hundred years ago the emotional origin or urticaria and eczemas was recognized, as well as the psychic cure for warts.

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15. Wilson,[1] p. 485.
16. Wilson,[1] p. 480.
17. Wilson,[2] p. 152.
18. Wilson,[2] p. 192.

PRIMARY PUSTULAR GONORRHEA OF THE SKIN

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AND
DAVID F. BRADLEY, M.D.
NEW ORLEANS

PRIMARY cutaneous infection by Neisseria gonorrhoeae, without urethritis, following sexual contact is an unusual venereal disease entity generally overlooked. A patient with a penile ulceration appearing 35 days after contact was proved, by Lowry and Franks (1943),[1] to have gonorrhea resistant to sulfathiazole treatment but cured by cauterization of the lesion. Kroll and Cohart (1944)[2] reported two proved cases of primary penile ulceration due to N. gonorrhoeae, in which treatment with sulfathiazole was successful. A fourth patient was successfully treated with crystalline penicillin G in peanut oil, 300,000 units daily for seven days, by Scott and Thomsen (1950).[3] A patient with gonorrheal pustule on the penis was treated successfully with 2.0 gm. of aureomycin by Marmell (January, 1952)[4] after failing to respond to 2,900,000 units of penicillin. Readers are referred to the article by Kroll and Cohart for an extensive bibliography of French and German papers dealing with primary gonococcal invasion of the skin.

REPORT OF A CASE

J. D. P., a 22-year-old, white man, foreign seaman, was seen in the Dermatology Out-Patient Department because of penile lesions (Fig.), which he stated had appeared 7 days after sexual exposure and 14 days before consultation. He denied having any urinary tract or joint symptoms or any previous history of venereal disease. He had received three large white tablets, presumably sulfonamides, every two hours for three days on shipboard prior to admission, without any improvement.

The patient was a well-developed, well-nourished, white uncircumcised man, in whom positive physical findings were limited to two small pustules, each averaging 2 mm. in diameter and 3 mm. in depth, present on the coronal sulcus adjacent to the frenulum, with a similar pustule on the opposite side of the frenulum. There was no erythema present, associated either directly with the lesions or with any surrounding tissue of the penis or foreskin. Cream-colored, purulent material was easily expressed from these pustules by light pressure. The inguinal nodes were discrete, firm, and nontender bilaterally. The cream-colored material expressed from the pustules

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1. Lowry, E. C., and Franks, A. G.: Primary Gonorrheal Cutaneous Infection, Am. J. Syph. **27**:428, 1943.

2. Kroll, M. M., and Cohart, E. M.: Primary Cutaneous Gonococcal Lesions of the External Male Genitalia, Am. J. Syph. **28**:320, 1944.

3. Scott, M. J., and Thomsen, J.: Primary Cutaneous Neisseria Gonorrhoeae Infection, Am. J. Syph. **34**:262, 1950.

4. Marmell, M.: Primary Cutaneous Infection with Neisseria Gonorrhoeae, Am. J. Syph. **36**:88, 1952.

revealed Gram-negative intracellular Diplococci. These organisms failed to grow on plain agar at 37 C. or at room temperature, but grew abundantly on chocolate medium in a 10% carbon dioxide atmosphere, showing morphologically typical Gram-negative diplococci giving a positive oxidase reaction and sensitive, in vitro, to the common antibiotics. Several attempts to test the organisms on carbohydrates enriched with ascitic fluid were unsuccessful because of contaminants that were not seen on the original chocolate plates. A culture of these organisms was then sent to the Communicable Disease Center, Laboratory Services, United States Public Health Service, at Chamblee, Ga., where a definite diagnosis of N. gonorrhoeae was made.

Three dark-field examinations of the lesions were negative, as were the serological Kolmer test and the VDRL slide test for syphilis. The Frei and Ducrey skin tests for lymphogranuloma venereum and chancroid, respectively, were negative. Two blood cultures revealed no growth. Sterile voided urine revealed 3 to 5 pus cells per high-power field, and culture was positive for Staphylococcus aureus. Hemogram, sedimentation rate (Wintrobe tube), and hematocrit were within normal limits. Several attempts at prostatic massage were unsuccessful in obtaining prostatic secretion for study.

Primary gonococcal pustules on the coronal sulcus of the penis.

Four days after admission, two of the pustules were excised for pathological study in order to rule out the possibility of aberrant urethral tissue or Tyson's glands. The base of the lesions excised was then cauterized with 2% silver nitrate solution and painted with 2% gentian violet. The patient was then given aqueous penicillin G, 100,000 units, and procaine penicillin G, 300,000 units, followed by three days of procaine penicillin G, 600,000 units, daily for a total of 2,200,000 units. Histological section of the lesions excised revealed partially denuded stratified squamous epithelium, beneath which was granulation tissue containing numerous small vessels and a rather dense infiltration of macrophages, polymorphonuclear leucocytes, and some lymphocytes. No glands were seen in any of the sections. Brown-Brenn bacterial stains revealed the presence of numerous Gram-negative intracellular diplococci. Gonococcal complement-fixation study could not be obtained. Following the penicillin therapy, a direct Gram stain smear of the remaining pustule was negative and the patient was discharged. However, a chocolate agar culture reported sometime later contained Gram-negative diplococci. It was impossible to contact the patient for follow-up studies.

Assistance was given by Mr. Ruffin LeBrane, surgical attendant, and Miss Edna Isom, bacteriologist.

COMMENT

The skin has long been recognized as a formidable barrier to N. gonorrhoeae. However, European physicians seem to be aware of the presence of primary cutaneous involvement with this organism to a greater extent than do American medical circles.

A sixth proved case of primary cutaneous infection with N. gonorrhoeae following sexual contact is reported, with in vivo resistance to penicillin therapy presented.

It is emphasized again that all pustular lesions of suspected venereal disease involving the external genitalia should have bacteriological studies for N. gonorrhoeae.[2]

PERSONALITY FACTORS IN ADULT ATOPIC ECZEMA

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THIS STUDY represents a collaborative effort between dermatologist and psychiatric team to study the personality and adjustment problems of adults with atopic eczema. Effort has been directed toward eliminating a selection factor prevalent in many other studies, that of grouping together a congeries of clinical syndromes under the general heading of "neurodermatitis." The cases studied in this series have met rigorous dermatological criteria for the diagnosis of atopic eczema. The purpose of this study has been to determine whether 30 patients with a similar dermatological disorder have in common significant personality attributes, prevalent emotional conflicts, and situational pressures, and whether these phenomena are associated with the occurrence and fluctuation of the eczema.

REVIEW OF LITERATURE

This dermatologic disorder probably was definitively described originally by Besnier,[1] in 1892. He termed it prurigo diathésique. There was a dearth of interest in the subject until the 1920's, when many articles appeared on the subject, applying various names to it. In 1930, Stokes and Pillsbury [2] published an article which is probably the cornerstone of the psychologic approach to the problem. Stokes and his associates have written voluminously on it since.

Becker [3] and Klauder [4] have espoused psychogenic factors in the etiology of many skin diseases, and Becker seems skeptical of the atopic concept of what he

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From the Department of Psychiatry: Staunton Assistant Professor of Psychiatry (Dr. McLaughlin), Instructor in Psychiatry (Dr. Shoemaker), and the Department of Dermatology and Syphilology, Assistant Professor of Dermatology (Dr. Guy), of the School of Medicine, University of Pittsburgh.

1. Besnier, E.: First Note and Preliminary Observations to Serve as Introduction to the Study of Prurigo Diathésique (Multiforme, Pruriginous, Chronic, Paroxysmal and Exacerbating Dermatidites of the Type of Prurigo of Hebra), Ann. dermat. et syph. **3**:634, 1892.

2. Stokes, J. H., and Pillsbury, D. M.: Effect on Skin of Emotional and Nervous States: Theoretical and Practical Consideration of Gastro-Intestinal Mechanism, Arch. Dermat. & Syph. **22**:962 (Dec.) 1930.

3. Becker, S. W.: Dermatoses Associated with Neurocirculatory Instability, Arch. Dermat. & Syph. **25**:655 (April) 1932.

4. Klauder, J. V.: Psychogenic Aspects of Skin Diseases, J. Nerv. & Ment. Dis. **84**:249 (Sept.) 1936.

calls disseminated neurodermatitis. Brunsting,[5] in the introduction to his article on atopic eczema, pointed out the sharp division of opinion among many writers as to whether the nervous system or sensitivity to proteins looms largest in the pathogenesis of this disease.

Rogerson [6] in a behavior study of 30 children who had both asthma and "prurigo" found certain personality features prominent among them. He applies the terms overanxious, unselfconfident, afraid, insecure, tense, restless, and irritable in describing these children. In many of them, as observation continued, overaggressive, overactive, and domineering tendencies appeared. Psychologic testing demonstrated that as a group they were above average in intelligence. Greenhill and Finesinger [7] studied 32 adult atopic eczema patients from the psychiatric standpoint. They concluded that, as a group, their patients exhibited more psychoneurotic symptoms than did control groups, and they observed a noteworthy absence of hysterical manifestations. Hostility, suppressed anger, and depression were frequently displayed by almost all of them.

Lynch [8] and co-workers, in a psychobiologic study carried out jointly by a dermatologist, an allergist, and a psychiatrist, found that all their patients had certain personality factors in common. Suppressed resentment, tension, above-average intelligence, and self-assertiveness were the most notable. They also noted an almost uniform absence of anxiety and hypochondriasis. Walsh and Kierland [9] described their experiences with psychotherapy in a group of patients with "disseminated neurodermatitis." They had successful results in 9 out of 15 cases. The erudite, readable article of Williams [10] has recently stirred up the question again. It should warn all students of atopic eczema against seeking a single etiology for it. He concludes that the factor of maternal rejection is operative in a large number of these cases and offers suggestions in the management of young patients on this basis.

DESCRIPTION OF STUDY

Thirty cases of adult atopic eczema, 9 male patients and 21 female patients, were selected for evaluation. All but four mild cases were judged by the dermatologist to range from moderate to severe in the extent of their involvement. Evaluation consisted of from two to five psychiatric interviews, a social-situation appraisal by the social worker, including, in 28 of the cases, an interview with spouse, mother, or sibling of the patient, and, in 27 cases, a battery of psychological tests consisting essentially of the Wechsler-Bellevue intelligence scale, the Rorschach test,

5. Brunsting, L. A.: Atopic Dermatitis (Disseminated Neurodermatitis) of Young Adults: Analysis of Precipitating Factors in 101 Cases and Report of 10 Cases with Associated Juvenile Cataract, Arch. Dermat. & Syph. **34**:935 (Dec.) 1936.

6. Rogerson, C. H.: The Psychological Factors in Asthma-Prurigo, Quart. J. Med. **6**:367 (Oct.) 1937.

7. Greenhill, M. H., and Finesinger, J. E.: Neurotic Symptoms and Emotional Factors in Atopic Dermatitis, Arch. Dermat. & Syph. **46**:187 (Aug.) 1942.

8. Lynch, F. W.; Hinckley, R. G., and Cowan, D. W.: Psychosomatic Studies in Dermatology: Psychobiologic Studies of Patients with Atopic Eczema (Disseminated Neurodermatitis), Arch. Dermat. & Syph. **51**:251 (April) 1945.

9. Walsh, M. N., and Kierland, R. R.: Psychotherapy in the Treatment of Neurodermatitis, Proc. Staff Meet., Mayo Clin. **22**:578 (Dec. 10) 1947.

10. Williams, D. H.: Management of Atopic Dermatitis in Children: Control of the Maternal Rejection Factor, A. M. A. Arch. Dermat. & Syph. **63**:545 (May) 1951.

and the Thematic Apperception Test.[11] Five patients underwent extensive psychotherapy lasting for at least one year, with interviews at weekly intervals. Four others were exposed to brief psychotherapeutic efforts lasting only a few months.

DESCRIPTION OF PATIENTS

Socioeconomic Factors.—The age of these patients ranged from 14 to 42, averaging 21.1 years (median, 20 years). Twenty-nine were white, one, Negro. Twenty patients were economically marginal or dependent on the community and the other 10 comfortable. Nineteen patients were single and nine married.

Educational Level.—There were 2 college graduates, 3 with one year of college, and 10 high school graduates in the series. The rest had either dropped out at various points in the first 12 years of school or, in five instances, are still students.

Allergic History.—A positive family history of allergy (exclusive of atopic eczema) was discovered in the family medical history of 11 patients, manifested as asthma, rhinitis, or dermatitis. Seven patients had a mother, sibling, or child who had a definite case of atopic eczema. The patients themselves showed no significant trend in terms of a positive history of asthma, rhinitis, or urticaria. In 18 the findings were quite negative, as against 12 who had asthma or rhinitis alone or in combination.

Course of Eczema.—The eczema began in infancy for 11 patients, in childhood for 13, and in adolescence or later for the remaining 6. In the majority of cases the active eczematous condition was intermittent in occurrence, once the first attack had occurred. In those instances in which the eczema had persisted for more than a month or so in infancy, the condition tended to be present to some degree thereafter, in some cases accompanied by or alternating with asthma or rhinitic attacks. Variation in severity of eczema in response to seasonal change was not striking—only three patients felt that winter was definitely a troublesome time and five others that summer weather made them worse. The rest noted mainly that excessive warmth at almost any time, regardless of season, tended to increase the itching and redness.

Psychiatric Diagnosis.—In the terms of psychiatric diagnosis all these patients could be classed as suffering from a psychophysiological skin disorder. Four patients maintained a borderline psychotic adjustment for which institutional care was occasionally required. The other 26 patients showed neither psychosis nor classic neurotic symptomatology, but instead showed varying degrees of personality disorder, whose characteristics will be enumerated below.

Personality and Patterns of Adjustment.—As a group, these 30 patients showed a number of striking similarities of attitude and behavior. Table 1 summarizes the interview behavior of the group during the appraisal period. All were guarded and reticent, tense and passively immobile. All denied ever experiencing strong feelings of love or hostility and denied reaction to the appraisal situation. As a group, the female patients gave the superficial appearance of boredom and indifference, whereas the male patients seemed eager to be liked, were ingratiating, and were more open in revealing their dependence. With few exceptions, they were poker-

11. Social studies in this series were done by Mary T. Darst, M.S.S., and psychological testing was under the supervision of Pearl B. Diana, Ph.D., both of the Staunton Clinic and University of Pittsburgh.

faced, excepting for the eyes, which alone expressed feeling described by different interviewers as "anxious and fearful" or "angry and hurt." Many of those who cried, and others who did not, expressed strong reluctance to cry and shame in doing so. Furious scratching and vivid flushing by patients of both sexes were the usual accompaniment of an otherwise flat and unemotional discussion of stressful and disturbing subjects. Open anger or resentment expressed toward the interview situation was rare—in the few instances in which such expression occurred there tended to follow an obvious reduction in or cessation of scratching. It was the exception to elicit complaints about life situation or personal adjustment excepting in terms of eczematous disablement. While proportionately more male than female

TABLE 1.—*Interview Behavior*

	Female	Male
Cases, no.	21	9
Interview behavior		
Relaxed and communicative	0	0
Guarded and reticent	21	9
Crying	13	1
Scratching	15	5
Flushing	14	6
Open anger or resentment	2	1
No expressed discontent regarding life situation and adjustment	13	5
Complaints other than eczema	4	4
Complaints of anxiety or tension	4	4

TABLE 2.—*Family Relationships in Female Eczema Patients*

Mother		Father	
Alive	19	Alive	16
Dominant	18	Dominant and alcoholic	3
Remote or cruel	9		
Preferred sons	9	Depreciated and subordinate	18
Defeated by husband and responsibilities	3		
Patient dependent	20	Patient dependent	0

patients felt tension or anxiety as such, the number was actually small in both instances. Physical disorders other than allied atopies were conspicuously absent.

For purpose of clarity, further description is presented in terms of the two sexes.

FEMALE ECZEMA PATIENTS

Family Relationships.—In none of the 21 patients could there be demonstrated an emotionally healthy family relationship. For the majority of these female patients their relationship to mother was clearly of crucial significance (Table 2). It is noteworthy that the mothers of 19 of the patients are still alive and an active influence in the patient's life pattern, regardless of the patient's age or marital status. Eighteen patients have a mother who is dominant, stronger, and more aggressive than the father, and who has operated in a rejecting fashion toward the patient throughout her lifetime. The kind of rejection shown by these mothers was an obvious one—either outright cruelty, oppressive domination, preference for other children, or smothering solicitude.

In the 13 instances in which the mother also was interviewed, and in other instances in which the spouse or a sibling was interviewed, evidence was obtained which amply confirms these impressions. On a number of these occasions it was possible to observe directly the interaction between the mother and daughter, in which the patient's docile acceptance of open criticism, sarcastic belittling, and tenacious dominance was striking. There could be seen a reciprocal hostile relationship, with the patient struggling to maintain an air of calm indifference. The eczema seemed often to exact attention from the mother and at the same time punish her by the excessive demands of the disease.

The father of these same 18 patients are clearly seen to have occupied a secondary and depreciated position in the family unit. While in many cases kindly and well-intentioned, they were either absent or so preoccupied with outside responsibilities and overshadowed by the wife to whom they were subservient that they did little to establish themselves as worthwile in the eyes of their daughters. The three patients whose parents differed from the group pattern described the father as cruel and

TABLE 3.—*Habitual Handling of Aggression*

	Female	Male
Cases, no.	21	9
Direct action	1	0
Speech	14	3
Denial	16	9
Stubbornness	20	6
Overconformity	18	6
Compulsiveness	11	1
Itch-scratch complex	20	8
Flushing	14	6
Crying	16	4
Masochistic behavior	12	5
Depression	14	8
Mild to moderate	10	7
Severe	4	1

sadistic, chronic alcoholic, who used physical brutality in dealing with wife and children. Mother, although beaten down and intimidated, was still looked upon by these patients as essential to their security.

Habitual Attidudes Toward Parents and Parent Substitutes.—With the exception of these three patients with alcoholic fathers and two other patients who in their psychotic episodes burst forth with much feeling against their mothers, the group as a whole tended to say only the right things about their parents. However, flushing, crying, scratching, and tension conspicuously occurred at those times when mother and topics related to her were uppermost in the interview.

Twenty patients of the group exhibited an extreme and insecure dependence upon their mother, including the patients whose fathers were brutal and dominant. The one exception managed in her middle years to "stop bowing and scraping to mother"; interestingly, with this move her skin cleared and remained clear for several years, until reality pressures became overwhelming, and need for help became acute.

For the 10 married women marriage had little effect upon this closeness to mother—they either lived in with the parent or near by, continuing both physical

and emotional closeness to her. In dealing with mother, these 21 patients reflect their fear and uncertainty about her by strained efforts to deny their hatred, by outward docile acceptance of her unpredictable behavior (Table 3).

Overconformity to the demands of mother and other authority figures was habitual in 18 patients, often coupled with subtle negativism. Open anger was not displayed toward the mother by any patient. One patient, whose eczema appeared in infancy and lasted three or four years, as a child was openly rebellious and defiant in dealing with mother and schoolteachers. During this period she had no eczema. In adolescence she grew conforming and docile; her eczema reappeared.

Flat denial of their own anger or aggressive impulses was expressed by 16 of the patients, and although 14 of them occasionally voiced their grievances, this exclusively verbal expression was tantrum-like, lacked real conviction, and afforded them little relief from tension. Instead of open expression of anger, varying combinations of substitutive expressions were used, as indicated in Table 3. The prevalence of depression, occurring usually in transient episodes, was strikingly evident.

TABLE 4.—*Sexual Adjustment in Female Eczema Patients*

Onset or exacerbation of eczema at menarche		11
Subsidence of eczema at menarche		1
Single	11	
Married	10	
Divorced	2	
Unstable	7	
Tranquil	1	
Comfortable sex adjustment		1
Frigid or dyspareunic		9
Sexual identification		
Feminine	6	
Masculine	15	

Sexual Identification and Sexual Conflicts.—Without exception, these 21 patients were reluctant to discuss matters of sexual adjustment. Regardless of age or marital status, only one patient gave evidence of being comfortable in her sexual life. Eleven patients had suffered the onset or exacerbation of their eczema with menarche. Love affairs, marriage, pregnancy, and childbirth conspicuously precipitated exacerbations of eczema (Chart 1). Of the 10 marriages, 2 have ended in divorce, 7 were stormy and unstable, and only 1 showed evidence of tranquillity. This same patient, whose eczema was mild and intermittent, was also the only one who admitted to a satisfactory marital adjustment, the other married patients being either frigid or dyspareunic.

The unmarried patients showed either marked avoidance of sexual situations, or tension, anxiety, and vasomotor skin changes incidental to such activities as they could permit themselves.

The erotic strivings of these patients showed evidence of having been repressed and transformed into the conflictual immature substitutes of inhibited looking and exhibiting and tactile sensuousness. Sex and aggression seemed equated. Sexual masochism was demonstrable in the actual sexual adjustment of four of the patients, who also used their scratching as a partially pleasurable outlet for erotic tension. All but two of the patients showed considerable conflict about their exhibitionistic

tendencies, so much so that they rarely were comfortable in attracting attention to themselves even to the extent that is culturally acceptable for a female person of our society. Instead, they tended to flush readily, to become tense, or, in a few instances, dizzy and confused in situations which stimulated show-off impulses.

Beneath this outward avoidance and denial of sexuality the following dynamics were discernible by implication and by the psychological testing data: Fifteen patients were either extremely masculine or markedly bisexual in their sexual attitudes. The other six were feminine. All were disturbed by their own sexual feelings, relatively infantile in psychosexual outlook, and striving to solve their conflict by seeking a close, secure, and passive relationship to mother or a substitute for her.

Male Eczema Patients

Family Relationships.—Each of the nine patients clearly was currently involved in a life situation in which a striking degree of passive-dependence upon a parent

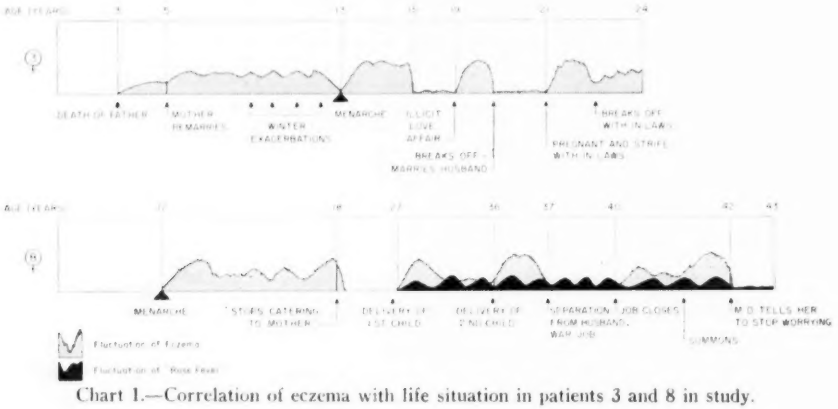

Chart 1.—Correlation of eczema with life situation in patients 3 and 8 in study.

or parent surrogate was manifest. This key figure was primarily maternal. A disturbed family situation was found to have been the rule in these cases, and three of the patients were products of tempestuous, broken homes. In general, the mothers in this group of patients were markedly ambivalent, inconsistently rejecting, indulgent, and overprotective. Relative rejection had been operative in at least four of the cases, in which a mother had favored a sibling openly, and, in these instances, the patient chafed under his inability to compete with the more fortunate sibling. In five cases, circumstances threw mother and patient closely together for long periods, with no father in the picture, and the conflictual stress of excessive erotic stimulation was evident in the relationship.

The fathers of five patients were openly rejecting and abusive toward the son. In the three cases in which divorce had occurred, the fathers took no interest in the patients subsequent to the marital break. The wish was apparent on all levels in three cases to have a passive, good-boy relationship with the dominant and successful father. The same sort of striving toward father figures was seen enacted in the life situations in those cases in which the father relationship had been disruptive and discordant. Only one patient, who was under hospital treatment for mental illness

when studied, was able to verbalize hostility toward his father. As a group, these patients were unable to cope with male aggressiveness, and masculinity in others represented a continually threatening force.

Habitual Attitudes Toward Parents and Parent Substitutes.—There is ample evidence (Table 3) to show that these nine patients, like the female patients, were beset with insoluble conflict in regard to their hostility and aggression. In no case could successful handling of these feelings be seen. They were even less prone to verbal aggressiveness than were the female patients. These patients avoided competition, rather openly sought for a secure, protective environment, and despite a transient show of masculine striving for self-sufficiency, educational failure and vocational stagnation were common. Denial of strong emotion was a common characteristic of these patients, yet anger-producing situations evoked itch-scratch reactions in all the patients. Again, as in the female patients, varying degrees of depression,

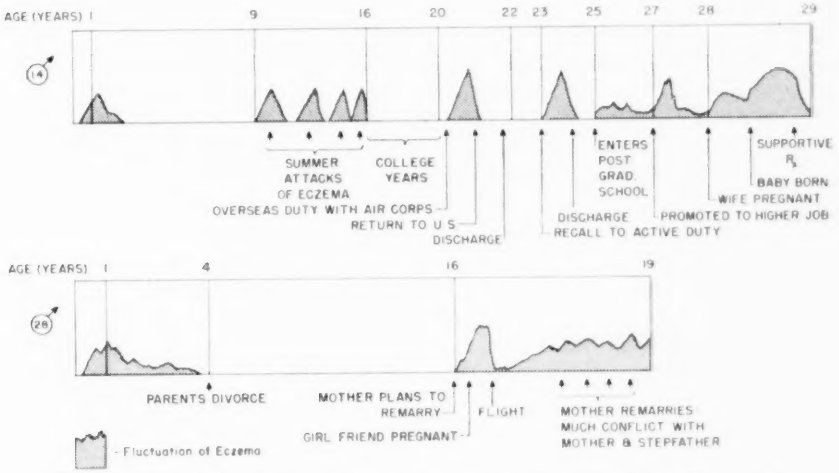

Chart 2.—Correlation of eczema with life situation in patients 14 and 28 in study.

only transparently masked by a variety of defenses and substitutive expressions, were easily demonstrated as transient but repeated reactions in nearly all the male patients. It is notable that three of the patients had a history of behavioral difficulty, expressed in truancy and fighting prior to the onset of the eczema but ceasing at this point. The various defenses of these patients broke down when immature security needs were threatened or denied. At these times, skin symptoms flared, the lesions were regarded as "badness," and depression was experienced. Chart 2 illustrates these tendencies.

Sexual Identification and Sexual Conflicts.—The nine patients were distinctly bisexual in their identification, with a relative predominance of feminine, passive trends. Guilt-laden homosexuality was overt and admitted in two cases, and latent homosexuality was evident in the functioning of three other patients.

Only one of the nine patients had married. Another patient, who displayed aggressiveness toward women in a sexual sense, was seen to be acting out the reaction formations of a Don Juan. One patient, while intensely attached to his

mother and involved in a sexual relationship with a teen-aged girl friend, committed suicide in apparent reaction to his guilt and the disapproval and rejection evoked in his mother by his clandestine affair.

COMMENT

It is rather clearly evident that these 30 patients cannot be classified clinically among the typical neurotic-reaction types. Instead, what we have seen is a long-standing personality disorder characterized by great passivity and excessive concern over acceptance by others, a deep but distrustful dependence upon a parental figure, a chronic seething hostility over repeated failure to obtain consistent dependent satisfactions from this person or anyone else, and an over-all inhibition of healthy aggressiveness. The eczema patient, bound in childish dependence upon someone stronger and thus utilizing essentially passive ways of meeting the pressures of living, characteristically responds to each new obligation or stress by becoming more passive and demandingly dependent. While more assertive persons would react by taking action to solve or diminish the stress situation, these patients tend to itch and scratch in fuming inactivity. The many life circumstances which mark the onset of the skin illness or its exacerbations are not characteristically castastrophes, such as deaths of key relatives, divorce, or severe accidents or disease. Instead, the precipitating events are those marking the normal sequence of growing adult responsibilities and maturation. The common denominator for these various situations is that each produces or threatens to produce an emotional separation from the parent or parental substitute.

The personality patterns common to the members of this series are not specific to this disease. They are features prevalent in the personality make-up of sufferers from arthritis, hypertension, colitis, asthma, and other psychosomatic disturbances. But it seems significant that these traits should so consistently be found in these 30 patients selected only on the basis of having the same disease. These people are burdened with a set of reaction patterns which impose chronic and severe strain upon their adaptive capacities. It is hard, exhausting work to contain and deny, to the extent seen in these patients, the strong impulses fundamental to human behavior. In a sense, they are worn out by what they do *not* do. An assumption often made in considering psychosomatic disorders is to the effect that the physical dysfunction has brought about the psychopathology seen in the sufferer from that illness. While this is partly true, it seems erroneous to apply this explanation to the dynamics herein described, in view of the episodic nature of the skin reaction and its frequent appearance for the first time only when the person is in adolescence or adulthood, with his personality patterns by then rather well set.

The crucial question centering around the factors leading to the selection of the skin as the dominant response organ cannot clearly be answered from such data as these. It seems evident that these patients have an unusually sensitive and hyperactive skin for reasons that are undoubtedly multiple. One interesting yet speculative point is the finding, in dream material, psychotic productions, and psychological testing, that these patients retain an unelaborated intensely sensuous wish for skin contact. This may reflect an inherited skin hyper-reactivity; whether or not this is so, there can be seen in the cases herein reported a pattern of dynamic circumstances, important in the occurrence and perpetuation of the eczematous state, which can be summarized as follows:

The patient from early childhood seems to have been faced with a struggle to gain satisfaction for his early needs for security and readily given maternal love from a mother who could not or would not satisfy those needs, and who, furthermore, would not permit him opportunity to learn increasingly effective expression of his strong feelings of aggression and affection. Set in a pattern of passive adaptation and denial of his own impulses, the patient continues into adulthood wishing to be protected, securely loved and freely given to, without being asked anything in return. Whenever these wishes are frustrated or demands made by love object or environment, the patient's hostility rises to new heights, with impulses to force the giving of that which is sought, to lash out destructively at the frustrating person. But this show of force is out of the question, due to his dependence, weakness, fear of losing what he has, and fear of retaliative desertion or further deprivation. So, very little of this conflict is revealed in overt action or speech. Instead, his passive-receptive wishes are expressed on a primitive physiological level in the exaggerated form of those skin reactions which are characteristic of the hungry, feeding infant: flexural and facial erythema and perspiring. The hostile, destructive element in his conflict is acted out in the substitutive mode of scratching and crying, both being a turning of the anger against himself in a mechanism seemingly related to depression. As in depression, the hostility that was actually felt toward someone or something else is turned inward in a guilty, self-punishing fashion which can be seen as a masochistic coercion to force forgiveness and discharge guilt: "Be good to me, for see how I suffer and punish myself for the badness in me" phrases this mechanism. Such a dynamic pattern, begun early in life, lends itself well as the substratum of such later psychic elaborations as masturbatory equivalents, masochistic sexual activities, and sadistic preoccupations. That this linking of the eczema-scratch phenomena to depression is not merely a theoretical point is demonstrated by the high frequency of at least brief depressive episodes in these patients, by the one suicidal case, and the prominence of severe depression in those patients whose personality incapacitation was severe enough to require custodial care. Indirect evidence of the inter-relatedness of eczema, depression, and hostility is seen in the findings that the occasional overt act of hostility could cause a reduction in the severity of the eczema and a lightening of mood, and that the depression of the eczema patient lifts rather readily once his environment can be induced to satisfy his needs. It is conceivable that the eczema-scratch complex tends to bind hostilities and guilt which could otherwise potentially develop into full scale self-destructive tendencies.

Therapeutic Implications.—While the purpose of this study has not been that of demonstrating the usefulness or futility of the psychotherapeutic approach, certain impressions about case management have been developed. The majority of the patients of this series do not seem suited to insight-producing or "depth" psychotherapy, by reason of their strenuous denial of their own emotions, their passive negativism, and the frequent fragility of their personality adjustment. Better suited to the needs of these patients are those psychotherapeutic techniques involving strong emotional support and encouragement from the therapist and fairly active intervention by him into the situational tangles in which the patient is so apt to get himself enmeshed. Such an approach, emphasizing reduction of environmental pressures, opportunity to ventilate, and dependable emotional support can, in many instances, bring about remission of symptoms in a matter of several weeks.

Similar dynamics underlie the response of many of these patients to hospital care. In addition to whatever specific efficacy the treatment regimen might have, hospital care and the attentions of the physician gratify many of the dependent wishes of the patient, at times give him haven from his situational stresses, and often force his environment to serve him better as a dramatically ill person than it did when he was merely scratching at home. If this environmental improvement persists after his discharge, the patient is far more likely to sustain his improvement than if he returns to the same unhealthy set of circumstances.

It is strongly indicated by these data that emotional support and environmental adjustment be included in the therapeutic efforts of the dermatologist or other physician handling these problems. Rather clearly, it is apparent that the effectiveness of treatment of any nature is going to be importantly affected by these personal and environmental factors and that where these are not at least recognized the efficacy of any treatment technique or regimen cannot accurately be evaluated.

CONCLUSIONS

1. The syndrome of atopic eczema represents a psychophysiologic skin disorder occurring in conjunction with primitive polymorphous personality patterns, in which there are evident a minimum of classic psychoneurotic characteristics.

2. The general pattern of personality defect seen in these patients is similar to that described for a variety of psychosomatic disorders, namely, excessive passivity and clinging dependency, coupled with a crippling inhibition of aggressive and erotic drives.

3. The more specific pattern of the eczema-pruritus-scratch complex seems importantly related to the dynamics of depression, even when given specific elaboration in the service of conflictual erotic and aggressive strivings.

4. A close temporal relationship can be demonstrated repeatedly between stressful life situations and the occurrence or exacerbation of atopic eczema in the patients of this series. Characteristically, these life situations are not catastrophic, but, instead, reflect the normal complications of maturation. The common factor to the various situations is that each represents an actual or threatened disruption of the emotional ties between patient and the object of his excessive dependency.

5. In the life patterns of the patients of this series there could be demonstrated a chronic and persisting unhealthy child-parent relationship, characterized by a relative or actual rejection of the patient by the parents, chiefly the mother.

HEREDITY OF MULTIPLE BENIGN CYSTIC EPITHELIOMA

"The Indiana Family"

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EVANSVILLE, IND.

MULTIPLE benign cystic epithelioma is frequently a hereditary affection that begins most commonly at the age of puberty. The lesions usually occur on the face and consist of numerous pinhead- to pea-sized, rounded, yellowish or pink nodules. The disorder has been described under the titles of trichoepithelioma papulosum multiplex, epithelioma adenoides cysticum, and acanthoma adenoides cysticum.

ANCESTRY OF THE INDIANA FAMILY

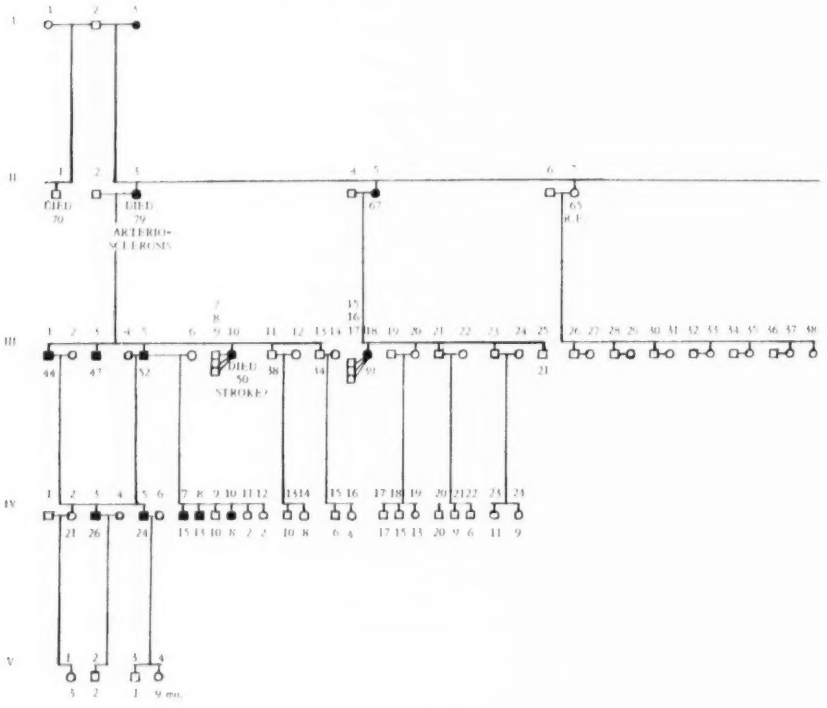
Shortly after the expedition of George Rodgers Clark, 1778-1779, a family destined to make dermatologic history settled in Princeton, Ind. The family name was Wh—, and they had migrated from the Carolinas. Little more was learned about their ancestry. Soon a person by the name of Wa— entered the outpost. He came from Ohio and was said to be of Scotch-Irish descent. According to rumors from his descendants "a lot of Indian blood" had accrued in his veins. This would not be surprising in view of conditions in those times. The Wa— siblings remembered that their mother had "bumps" on her face. It was also thought that there were a number of aunts and uncles on the maternal side. The subjects interviewed were vague as to their whereabouts. One descendant was found, B. W. C., a woman born in 1900. Tumors characteristic of multiple benign cystic epithelioma affected her nose and nasolabial folds. A spinster daughter, aged 39, did not show any lesions. B. W. C. had three sisters and two brothers, who, she stated, did not have the condition. She declined to disclose anything more about them. One sister was said to have 12 living children.

One of the Wa—s knew of another person some miles away who had similar lesions on her face. Any relationship was denied. This woman, E. S., aged 49, was severely affected with tumors and milia-like lesions. She was an orphan and did not know the names of her parents. She thought she was born in a little town about eight miles from Princeton. She had had eight children, two by the first marriage and six by the second. Her husband advised her not to have any tests, and she declined to aid in contacting her children. B. W. C. was known to be a descendant of the Wh—s. Apparently, it was this stock that brought the affection to southern Indiana.

The genealogy of the Wa— family is presented in Figure 1. The desire of Subject IV-52 to have the lesions treated led to the recording of 40 cases. Thirty-one subjects were examined. Seven subjects permitted biopsies of lesions for histologic study.

TRANSMISSION

An unusual dominance for multiple benign cystic epithelioma was found in this family. Subject III-5 transmitted the affection through two females. Males predominate, with a ratio of 2:0 in the first marriage, and 2:1 in the second marriage. The dissimilar twins IV-11 and IV-12 will be interesting to watch for the appear-



R.E.—Refused Examination. P.—Pregnant

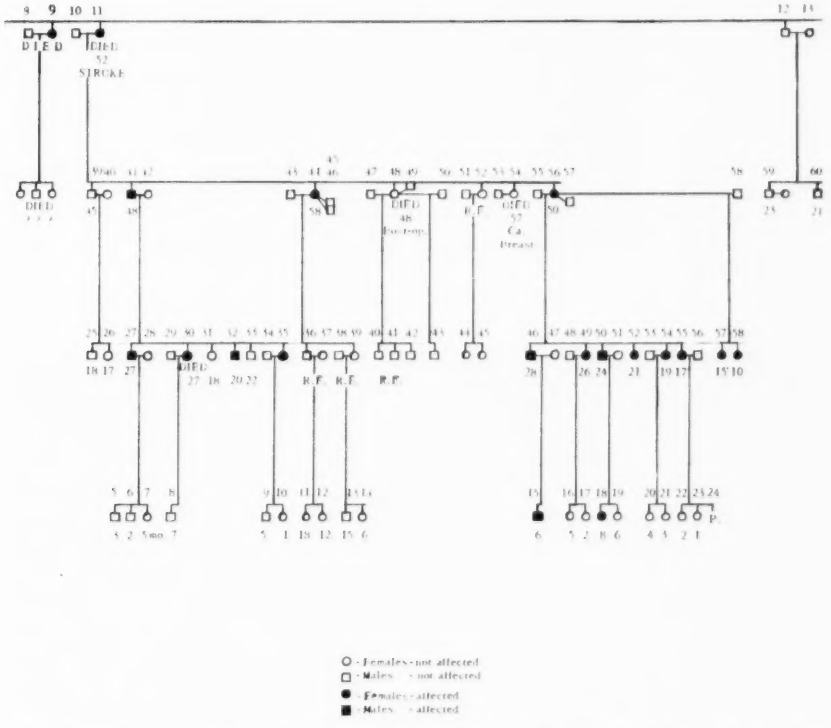
Reported affected—I-3, II-9	2 cases
Identified by Photograph—II-3, II-11, III-10, IV-3, 5, 30.	6 cases
Examined by Dr. J. R. Rogin—IV-35, V-9, 10.	1 case
Subjects Examined	28 cases
Total Subjects—Wa—Family	42 cases
Total Subjects Examined—Evansville area	25 cases

Dr. H. J. Muller, Dept. of Zoology, University of Indiana, gave helpful advice in preparation of this chart.

Fig. 1.—Chart showing genealogy of Wa—family. Since the manuscript was submitted for publication, six new cases have been found in the Indiana family. They do not appear in the pedigree because this would necessitate a redrawing of the chart.

ance of lesions. Passage through two females produced a male-to-female ratio of 4:1, with a possibility that this might become 4:4. Subject II-5 presented two tumors, measuring approximately 1 by 1 cm. and 5 by 5 mm., involving the left frontal hairline. The face and ears showed a profusion of milia-like lesions and marked

seborrhea. The affection was transmitted to one daughter, III-18, who had been married three times (pregnancies denied, question of sterility). She showed one tumor (Fig. 2), the replica of her mother's lesions and, in addition, typical lesions of multiple benign cystic epithelioma. The daughter had a mild seborrhea and the milia-like lesions were sparse, in sharp contrast with those of her mother. Subject III-41 (Fig. 3*A*) showed tumors and milia-like lesions. Both were transmitted with the same relative severity to two sons and one daughter. Subject III-56 (Fig. 3*B*) showed a severe tumor involvement but few milia-like lesions. The transmission was similar. Eight children, by two husbands, were all affected, a most unusual dominance. Goldman [1] encountered a similar heredity: a grandfather had two wives



and transmitted the affection through both. The ratio of males to females was 5:5. There is no consistent sex factor in the transmission of the disease. Fliegelman and Kruse,[2] too, found that all the criteria for dominant inheritance were fulfilled for multiple benign cystic epithelioma. No sex limitation was noted. The Wa— family showed no sex limitation. Multiple benign cystic epithelioma is transmitted as a regular dominant inheritance.

1. Goldman, H. J.: Multiple Benign Cystic Epithelioma: Report of Ten Cases in One Family, J. A. M. A. **115**:2253, 1940.

2. Fliegelman, M. T., and Kruse, W. T.: Hereditary Multiple Cystic Epithelioma, J. Invest. Dermat. **11**:189, 1948.

Fig. 2 (Subject III-18).—Tumor at right frontal hairline.

Fig. 3.—*A*, (Subject III-41), tumors and milia-like lesions. *B* (Subject III-56), severe tumor involvement but few milia-like lesions.

CLINICAL MANIFESTATIONS OF THE DISEASE

Description.—The best account of multiple benign cystic epithelioma found was that of Fordyce,[3] written in 1892. The disorder consists of numerous translucent and skin-colored tumors of pinhead to pea size or larger. The growths tend to be discrete, but grouping of lesions does occur. Subject III-5 looked as if masses of yellow peas had been pressed over the eyebrows and temple regions of the face. The tumors are firm and painless. Only the larger ones, of hazelnut size, show dilated capillaries. The tumors may be dome-shaped, flattened, or acuminate. Angular and pedunculated growths were found in the Wa— family. Subject III-41 showed pedunculated tumors hanging from the nasolabial folds. In Subject III-5 they hung from the eyebrows. This gave the face a striking appearance. A colleague happened to see one of the members, and his diagnostic thought was leprosy.

Distribution.—If bilateral lines were drawn from the concha of the ears to the lateral edge of the eyebrows, across the upper eyelids to the inner canthus, along the side of the nose to the upper lip, to the angles of the mouth, then to the midportion of the chin, the distribution of the affection would be patterned. The drawings by Goldman [1] are excellent diagrams of the location of the tumors. Only one subject, III-5, had lesions on the scalp and neck. On the scalp they were not raised, but could be palpated deep in the scalp tissue. A number of the subjects showed acuminate follicles over the upper midback and upper chest, but no tumors were found.

Primary Sites and Age of Onset.—The youngest subjects examined were 6 years old, V-15; 8 years, V-18 and IV-10, and 10 years, IV-58. The nasolabial folds showed the first lesions in three of these, and the upper eyelids, in one. Subject IV-46 was unusual in that only the concha of the ears were affected. The adults recalled the onset during grade school, before or about puberty. The crease molded by the cellular tissue forming the ala and the sesamoid cartilages of the nose was the commonest primary site for the development of tumors.

Changes in Lesions with Age.—There was a tendency for the tumors to increase in size with age. Tumors hardly noticeable in the teens reached 1 cm. in size in later decades (Subjects II-5, III-18, III-41, and III-56). Pedunculated tumors tended to develop with age. The massing together of lesions was most noticeable in the nasolabial folds, eyelids, temples, and ears. Subject III-56 had the external auditory canals partially occluded by tumor masses involving the concha and tragus of the ears.

Ulceration of Tumors.—In this group of subjects there was no tendency for the tumors to ulcerate or undergo malignant changes. Subject II-3 had died recently at the age of 79. I visited the physician who attended her. He recalled the tumors on her face but noticed no ulceration of any of them. Subject III-44 had an area of radiodermatitis 1 cm. in diameter at the left inner canthus of the eye. This resulted from radium therapy 16 years ago for an alleged epithelioma. No biopsy specimen was taken; thus this diagnosis was left in doubt. Existing lesions showed no unusual changes, and she claimed they had become smaller with the advancing years. She had just married for the third time. The male subjects mentioned cutting the tumors with razors many times and squeezing them. Yet no ulcerations were found, and there was no evidence of epitheliomata.

3. Fordyce, J. A.: Multiple Benign Cystic Epithelioma of the Skin, J. Cutan. Dis. **10**:459, 1892.

Seborrhea.—This was a constant and conspicuous feature of the Wa— family. The descendants of III-41 were the most severely involved. It is interesting and thought-provoking that the sebaceous glands in the biopsy material studied showed no nevoid or other discernible abnormality.

Milia.—Fordyce [3] noted that the faces in his patients had an oily appearance and that scattered among the tumors were smaller translucent lesions, which differed in no respect from ordinary milia. The surfaces of some of the larger tumors showed masses of these milia. Many of the affected members in my cases showed the ordinary milia, white globoid masses, like rice kernels, dotting the surface of the skin. They were easily shelled out by breaking the membranes enveloping their projecting surfaces. Differing from this common type of milia, another lesion referred to by Fordyce as milia-like was found. These lesions seemed to be part and parcel of the entity of multiple benign cystic epithelioma. Fliegelman and

Fig. 4.—Section of pedunculated tumor from same subject as that in Figure 3*A*. According to histologic description by Dr. Wilbert Sachs, within the cutis are several dilated follicles filled with horny material. Arising from these follicles and extending into the cutis are masses of basal cells. The palisade margin is intact. The cutis shows fibrosis. There is also a reaction composed chiefly of small round cells and showing plasma cells. The epidermis is thinned and flattened. The histologic diagnosis is multiple benign cystic epithelioma. The final review note in eight biopsy specimens disclosed that all the tumors arose from the follicle wall, and none of the tumors were associated with the sweat glands. There was no nevoid growth or any other abnormality of the sebaceous glands. (Photomicrograph by Dr. Francis W. Porro, pathologist, St. Mary's Hospital, Evansville, Ind.)

Kruse [2] commented that one of their patients remarked that he could press out of the lesions "cores of cheesy material." One of the Wa—s also indulged in this activity. Subject III-41 was one of the first examined. Many of the tumors showed whitish bodies making up their mass. As conspicuous as the tumors were discrete, white, pear-shaped bodies, the bulb end lying deep in the skin. The ostium projected slightly above the skin surface, which contained a whitish material, and imbedded therein were broken and fractured filaments. These milia-like lesions seemed to follow a transmission pattern in the affected subjects. Subject III-5 showed these translucent bodies in the tumors, but otherwise they were not con-

spicuous. This same pattern was reflected in his descendants. Subject II-5 presented a diffuse milia-like involvement with tumors. An affected daughter showed tumors but few milia-like lesions. Subject III-41, severely affected with tumors and milia-like bodies, transmitted them to two sons, IV-27 and IV-32, and two daughters, IV-30 and IV-35. The children not affected with tumors were also free of the milia-like bodies. Subject III-56 and her children did not show them.

A biopsy specimen of one of these milia-like bodies was obtained from the left side of the forehead of Subject IV-27. The section was studied further to observe the milia-like structure. At one side a typical keratinous nest was found lying in the epidermis. When this was traced through some 10 serial sections, it was found to open on the skin surface. Its keratinous material blended with the horn cells of the epidermis. Deep in the keratinous cyst was part of a hair filament. Only a few sebaceous glands were found. These did not appear unusual. The seborrhea in this subject was severe. During this study Subject III-41 had a hemorrhoidectomy. E. L. Fitzsimmons noted a profusion of perianal milia-like lesions. Keratinous nests were found in the sections, similar to those found in the specimen from the nose. The pathology of a pedunculated tumor, 5 mm. in diameter, from the right nasolabial fold in Subject III-41, is shown in Figure 4.

COLLATERAL DERMATOLOGIC FINDINGS IN AFFECTED SUBJECTS

The initial plans in this study called for complete physical examinations, blood cell counts and blood type determinations, and blood chemistry studies. Numerous appointments were made for the subjects, but they failed to keep them. Oral systemic reviews were made for each subject. Subject IV-27 had been in the armed service. He was alleged to have sustained an injury which was later diagnosed as Marie-Strümpell disease. No other major diseases were discovered. On the whole, the health of the subjects was average or above. Most of the subjects allowed a dermatological examination of the head, neck, mouth, torso, and extremities. A naevus anaemicus was found in Subject IV-58 on the right side of the chin. Subject IV-50 showed a palm-sized patch of spotty pigmentation on the right buttock, and Subject V-18 showed a granuloma annulare involving the right ankle. Subject III-56 had a hyperpigmentation affecting the sides of the neck. Subject IV-32 had a tinea versicolor. Fliegelman and Kruse[2] surveyed eight affected members in one family. They found a verrucous nevus in one and a café-au-lait-like spot in another. In spite of the severe seborrhea in the affected subjects, a history of acne was denied by all. No acne scars were found, and in only one subject, IV-7, were comedones evident. No predisposition to Fordyce disease was found.

PHYSICAL AND MENTAL TRAITS OF THE SUBJECTS

Twenty-six affected adults and children were surveyed. No systemic physical defects were found. The mentality was average. All subjects in generation IV had finished grade school, and most of them had finished high school. One was in college. One had been a beauty queen and the most popular girl in the freshman college class. Six subjects in IV had been in the armed services. A female was in the Women's Army Corps. All of them stated they belonged to a church. No instances of law violations were uncovered. There was no alcoholism, insanity, or history of seizures or convulsions. The subjects were industrious; some of them

had their own businesses. They described themselves as quick-tempered and emotional. The marriage rate showed a brisk turnover. In III, two women had each had three husbands. The hair color was black in 14 and brown in 10 subjects. No baldness was encountered. The eye color was brown in 12, blue in 4, and hazel in 8. One subject, IV-27, had a black spot in the left fundus, but he refused to see an ophthalmologist. Myopia was present in Subject III-41, his two sons, and one daughter. They also appeared to have optical photosensitivity. The teeth were normal in six subjects and very carious in two; false dentures were worn by three; a bilateral defect involving the upper canine and first premolar was present in four, and an overlapping of the first right incisor and first left incisor was shown in nine. One subject showed a marked stippling of the enamel. The complexions were dark in 18, medium in 3, and light in 3. The feet and hands were normal. One subject was a nail biter. The stature varied from 5 ft. 2 in. (157 cm.) to 5 ft. 8 in. (173 cm.). The weights ranged from 126 to 170 lb. (57 to 77 kg.). One subject weighed 180 lb. (82 kg.), and one, 200 lb. (91 kg.). The nose was of the straight type in all subjects. The ears were normal in contour and shape. All but one were right-handed.

COMMENT

If the fourth and fifth generations of the family in Figure 1 prove to be as prolific as the first and second, the next generation of dermatologists will be provided with many cases of multiple benign cystic epithelioma.

TREATMENT OF ECZEMA WITH CORTISONE OINTMENT

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IT HAS BEEN demonstrated that systemic administration of cortisone or corticotropin (ACTH) improves atopic eczema [1] in the majority of cases and that cessation of treatment is almost invariably followed by a relapse. Continued treatment with maintenance doses may delay such relapses but would be too costly and not without risk. For these reasons, systemic treatment of eczema with these hormones has not been recommended.[11]

Cortisone injected intradermally together with tuberculin has been shown [2] to suppress the skin reaction to tuberculin in sensitized persons and to decrease itching as well as the degree of inflammatory reaction. The question arose whether local action of cortisone could be utilized for the treatment of eczema. If it was possible to avoid large systemic doses and to apply cortisone to the skin in such a way that sufficient quantities would be absorbed locally, therapeutic results could be anticipated without undesirable side-effects.

The present communication deals with the treatment of eczema with various cortisone ointments, which was started in the fall of 1950.

MATERIAL AND PROCEDURE

Cortisone acetate is a crystalline substance of poor solubility.[3] Since fats permeate the skin easily via the hair shafts and oily gland ducts,[4] fat-soluble substances are

1. (*a*) Kanee, B.; Grant, J. H. B.; Mallek, J., and Eden, J.: ACTH in Atopic Dermatitis (Infantile Eczema) and Asthma, Canad. M. A. J. **62**:428, 1950. (*b*) DiGeorge, A., and Nelson, W. E.: Some Observations on the Use of Adrenocorticotropic Hormone in Atopic Dermatitis in Infancy, J. Pediat. **38**:164, 1951. (*c*) Randolph, T. G., and Rollins, J. P.: Adrenocorticotropic Hormone (ACTH): Its Effect in Atopic Dermatitis, Ann. Allergy **9**:1, 1951. (*d*) Feinberg, S. M.; Dannenberg, T. B., and Malkiel, S.: ACTH and Cortisone in Allergic Manifestations: Therapeutic Results and Studies on Immunological and Tissue Reactivity, J. Allergy **22**:195, 1951. (*e*) Cooke, R. A., and others: ACTH and Cortisone in Allergic Diseases: Clinical, Serologic (Electrophoretic), and Immunologic Studies, ibid. **22**:211, 1951. (*f*) Glaser, J.; Siegel, S. C.; Goldstein, J. D., and Meltzer, R. S.: Experiences with ACTH and Cortisone in Treatment of Asthma and Eczema in Infancy and Childhood, Ann. Allergy **9**:292, 1951. (*g*) Sulzberger, M. B., and others: Effects of ACTH and Cortisone on Certain Diseases and Physiologic Functions of the Skin: 1. Effects of ACTH, J. Invest. Dermat. **16**:323, 1951. (*h*) Downing, J. B.: The Use of ACTH and Cortisone in Dermatology, New England J. Med. **246**:56, 1952. (*i*) Sternberg, T. H.; Newcomer, V. D., and Linden, I. H.: Treatment of Atopic Dermatitis with Cortisone, J. A. M. A. **148**:904, 1952.

2. Vollmer, H.: The Local Effect of Cortisone on the Tuberculin Reaction, J. Pediat. **39**:22, 1951.

3. Gibson, A., Merck & Company, Inc.: Personal communication to the author.

4. Markowitz, M.: Practical Survey of Chemistry and Metabolism of Skin, Philadelphia, Blakiston Company, 1942, p. 64.

readily absorbed by the skin.[5] Cortisone, however, is not fat-soluble.[3] The ointments supplied[6] for clinical trial were suspensions of cortisone crystals in various bases containing between 3 and 25 mg. of cortisone per gram of ointment.

Better solvents to improve percutaneous cortisone absorption were looked for. Since 1 gm. of chloroform dissolves as much as 182 mg. of cortisone,[3] ointments were prepared by incorporation of cortisone solution in chloroform into vanishing cream or Hydrosorb. During levigation of the ointment, chloroform, which may irritate the skin, evaporates readily.

In 22 instances, use of cortisone and conventional treatment were combined. Cortisone diluted in chloroform was incorporated into ointments generally used by myself and my colleagues for the treatment of eczema, mainly "formula 241," containing resorcinol monoacetate 0.3, coal tar solution 2.0, boric acid 1.0, naphthalan 2.0, starch 8.0, and vanishing cream up to 30.0. Preparations as shown in Table 1 were used.

Thirty-five children with various forms of eczema were treated with cortisone ointment on one side of the body, the other side serving as a control. The age of the

TABLE 1.—*Preparations Used*

No.	Mg. Cortisone	Per Gram of Ointment Base	Treatments
1	3 (as solution)	Vanishing cream	2
2	5	An oxycholesterol-petrolatum ointment base (Aquaphor)	8
3	10	Greaseless base	2
4	10 (diluted in chloroform)	Hydrosorb	7
5	10 (diluted in chloroform)	Vanishing cream	20
6	10 (diluted in chloroform)	Formula 241	22
7	20	Polyethylene glycol (Carbowax) or hydrosorb	2
8	25	Polyethylene glycol, petrolatum, or vanishing cream	5

patients ranged from 1 month to 9½ years and the duration of eczema between one-half and nine years. The majority of the patients had been treated previously with various ointments and elimination diets with only temporary success or none at all. With the exception of one child, who was hospitalized, all patients were treated in the outpatient department.

If, for various reasons, immediate treatment with cortisone ointment appeared inappropriate, preliminary measures were taken. Oozing surfaces were treated with wet dressings until the acute inflammatory changes had subsided. Crusts were removed with salicylic acid ointment. Secondary infections of the eczematous skin were treated with antibiotics or ammoniated mercury ointment.

The half of the body serving as a control was treated with the ointment base (without cortisone) used in the cortisone ointment applied to the other side. Most children showed a symmetrical distribution of their eczema, with equal severity on the two sides. If there was an appreciable difference, the more severely affected side was treated with cortisone.

5. Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Physiologie der Haut, Berlin, J. Springer, 1929, Vol. I, Pt. 2, p. 6.

6. By Merck & Company, Inc., Rahway, N. J., and Schering Corporation, Bloomfield, N. J.

The mothers were usually instructed to apply the ointments gently to the skin three times a day. Where there were induration and lichenification, the ointment was rubbed in thoroughly. Bandages were not used.

Each treatment period lasted a minimum of one week, exceeding four weeks in only three instances. There were 68 treatment periods among the 35 children.

At each visit, I looked for differences in eczematous lesions of the two sides and formed an opinion before ascertaining which side was treated with cortisone. Then the mother was asked for her impression. If the two conformed, the result was noted as "improved," "unimproved," or "worse." In cases of disagreement or doubt, another pediatrician, without knowledge of the therapeutic procedure, was consulted and his judgment accepted. If the treated and the control skin area appeared equally improved, the condition was listed as "unimproved."

In cases in which the entire half of the body surface was treated with cortisone ointment, an absorption of cortisone in sufficient amounts to influence the control side had to be considered. To get an idea of the magnitude of such absorption into the circulation, 37 eosinophile chamber counts were done before, during, and after treatment. The method of Randolph, with phloxine-propylene glycol as diluent,[7] was used for the counts. Counts were done on nonfasting patients between 2 and 4 p. m.[8]

RESULTS

For a total of 68 treatment periods of at least one week's duration for 35 children, the results were as follows: 31, or 45.6%, were improved; 34, or 50.0%, were unimproved, and 3, or 4.4%, became worse. The improvements were of various degrees but generally unimpressive. It was mainly the degree of inflammation which appeared favorably affected. Pruritus decreased in only a few instances. None of the observed improvements had any characteristics not attainable with intelligent, conventional dermatologic treatment.

An attempt to classify the patients according to their clinical form of eczema and to determine the group most suitable for cortisone treatment was nonrevealing. Equally unsuccessful was a classification of the treatment periods according to the type of cortisone ointment used. Ointments prepared with cortisone solution in chloroform or containing higher cortisone concentrations did not prove superior to ointments containing cortisone crystals in suspension or lower cortisone concentrations.

Relapses after cessation of cortisone treatment were the rule. They could be prevented or delayed in a few instances if treatment with cortisone in an indifferent base was followed by cortisone in formula 241 and continued with the same ointment without cortisone. Rebound reactions after cessation of treatment were not observed.

It had been anticipated that small amounts of cortisone or none at all would be absorbed percutaneously. A maximum of 55 mg. of cortisone a day was applied topically; in the majority of instances the amount was less than 20 mg. Thirty-seven

7. Randolph, T. G.: Blood Studies in Allergy: I. The Direct Counting Chamber Determination of Eosinophiles in Propylene Glycol Aqueous Stains, J. Allergy **15**:89, 1944; Differentiation and Enumeration of Eosinophils in the Counting Chamber with Glycol Stain; A Valuable Technique in Appraising ACTH Dosage, J. Lab. & Clin. Med. **34**:1696, 1949.

8. Bonner, C. D.: Eosinophil Levels as an Index of Adrenal Responsiveness: Factors That Affect Value of Eosinophil Counts, J. A. M. A. **148**:634, 1952.

eosinophile counts were done in 15 different cases, showing the eosinophile response in 21 treatment periods (Table 2). A decrease of more than 50% was found in only three instances. In a fourth case (E. S., Table 2), a drop of the same magnitude followed an initial marked increase during treatment, so that the final value was higher than the count before treatment. On the other hand, increases of more than 100% in the eosinophile counts followed cortisone treatment in five instances. In the rest there were minor changes. There was no significant correlation between clinical improvement of the eczema and eosinophile response or between the extent of treated skin area and eosinophile response. There were no changes in body weight suggesting the accumulation of edema fluid.

TABEL 2.—*Eosinophile Responses to Treatment of Eczema with Cortisone Ointment*

Patient	Preparation: Mg. Cortisone/Gm. Ointment Base *	Site of Application † (Unilateral)	Duration of Application, Wk.	Eosinophile Count		Change, %	Clinical Result
				Before	After		
D. H.	10/VC	FAL	1	1,125	81	−93	Improved
	10/241	FAL	1	1,188	1,044	−13	Unimproved
J. L.	10/241	L	1	793	925	+16	Improved
M. J.	10/VC	F L	3	188	388	+107	Unimproved
	10/241	F L	3	388	575	+49	Unimproved
E. W.	10/241	F T	2	112	244	+118	Unimproved
E. S.	5/OPB	AL	1	38	81	+117	Improved
	10/241	AL	1	81	338	+317	Improved
	10/hydrosorb	AL	3	338	63	−84	Improved
	10/241	AL	8	63	125	+100	Improved
R. M.	5/OPB	F	2	650	687	+6	Unimproved
C. C.	10/241	FAL	1	382	281	−26	Improved
G. L.	10/VC	FALT	½	1,100	437	−60	Improved
	10/241	FALT	1	437	418	−5	Unimproved
G. B.	10/VC	FA	4	44	244	+458	Unimproved
E. B.	10/241	FAL	2	88	119	+35	Unimproved
K. C.	10/241	FAL	1	1,206	1,194	−1	Improved
N. M.	10/VC	F	1	5,500	3,331	−39	Improved
R. E.	10/VC	FA	5	250	231	−8	Unimproved
Y. R.	10/241	L	3	393	100	−75	Unimproved
J. P.	10/VC	F	5	1,069	1,338	+25	Unimproved

* VC, vanishing cream; 241, formula 241; OPB, an oxycholesterol-petrolatum ointment base.
† F, face; A, arm; L, leg; T, trunk.

COMMENT

Since systemic treatment of eczema with corticotropin or cortisone produces dramatic results in most cases,[1] the disappointing results with topical cortisone treatment call for an explanation. Cortisone topically applied might act by local absorption into the diseased skin layers or by percutaneous absorption into the circulation or both. The eosinophile responses seem to indicate that general absorption does not occur to any significant extent or with any regularity. The daily amounts of cortisone applied to the skin in most of our experiments would be insufficient to affect eczema even if they were quantitatively absorbed. Sternberg and co-workers [11] observed that all their adult patients with atopic dermatitis had relapses when intramuscular injections of cortisone were decreased below 75 mg. daily. All my patients received less than this amount and not by intramuscular but by topical administration.

To explain the unsatisfactory results one might suppose that local absorption of cortisone into the affected skin layers was insufficient. From the data available

about cortisone solubility,[3] it can be inferred that only minimal proportions of the crystalline substance go into solution and can be percutaneously absorbed in the given environment of skin secretions and ointment bases. This situation seems not to be improved by the use of chloroform as a vehicle. After its evaporation, cortisone is prone to precipitate again in the ointment bases, which are poor solvents.

Sternberg, Newcomer, and Linden [11] have recently reported on five adults with atopic dermatitis treated with cortisone ointments. Their results were as unsatisfactory as mine; little or no benefit was obtained. In two of their five cases, a pustular dermatitis developed within 48 hours on the cortisone-treated area. I encountered adverse effects after only 4.4% of the treatment periods; in these rare instances, the eczema became worse, but pustular dermatitis was not encountered.

SUMMARY AND CONCLUSIONS

Thirty-five children with atopic dermatitis were treated with cortisone ointments containing between 3 and 25 mg. of cortisone per gram of various ointment bases. Results from 68 treatment periods of at least one week's duration were observed.

Eczema was slightly improved in 31 (45.6%), was unimproved in 34 (50.0%), and became worse in 3 (4.4%) instances. Relapses followed improvement in almost all cases after cessation of treatment.

Eosinophile responses to 21 treatments with topically applied cortisone in 15 patients indicated little if any absorption of cortisone into the circulation.

It is concluded that local absorption was insufficient, too, in the majority of cases. With the cortisone ointments used, an effective concentration of cortisone was probably not reached in the affected skin layers.

The therapeutic effect of cortisone ointment in eczema does not exceed the results obtainable with conventional dermatologic treatment.

ADDENDUM

Using the same rigid controls, 2½% hydrocortisone ointment applied for three to seven days did not affect eczema in three children nor positive skin reactions to the tuberculin patch test in seven out of nine persons; in two of them the patch test reaction was diminished.

INFLUENCE OF LOCAL FACTORS ON CUTANEOUS INJURY AND HEALING

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IN A PREVIOUS paper [1] we made observations on the thresholds of various types of injury to the skin by varying the intensity of a stimulant while keeping constant the site, skin temperature, and blood flow. In the present paper we wish to report on some factors determining the type and severity of reaction, when the injury is to a fixed degree of heat. Clinically, it seems that injuries tend to heal at unequal rates at various sites, an impression we here put to experimental test. We also have examined some factors likely to be responsible.

METHOD

As in our previous work, we used the Guillemin instrument [1] designed for heat conduction by an electrode with a face of 25 sq. mm. and simultaneous indication of temperature and electrical energy necessary to obtain and maintain any given temperature. The subjects were normal volunteers and patients in bed with various disorders. The standard lesion was one made by the electrode touching the skin with its temperature raised to 54.4 C. within 30 seconds and held in contact at this level for one minute. The size and kind of injury resulting were noted after 24 hours and at the end of 10 days. The lesions were all small and required no dressing. We called the changes at 24 hours, "reaction to injury," and the ones at 10 days, "10-day reaction," and the difference between these two reactions, "healing."

RESULTS

Ten subjects received injuries at various sites of the skin (Table 1A). After 24 hours the lesions varied little as to size, but markedly in severity, though after 10 days there were also pronounced differences in size (Table 1B). Of the areas tested, the back and calf of the leg showed the highest rate of healing (Table 1C).

In the next series of experiments the subjects incurred four injuries spaced at regular intervals on the posterior surface of the leg from just below the popliteal space to the ankle; Site 1 was the highest, and Site 4 the lowest. Normally there is

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1. Guillemin, V.; Benjamin, F.; Cornbleet, T., and Grossman, M. I.: A Method of Quantitative Heat Application to Small Skin Areas at Controlled Temperature, J. Appl. Physiol. 4:920-924, 1952.

a gradient of increasing temperature up the leg, and, according to Horton and Sheard,[2] an increase in vascular tone down the leg. After 24 hours the lesions showed a difference in size and severity, with the greatest intensity at Site 3 (Table 1D). After 10 days the size of the lesions was progressively greater towards the peri-

TABLE 1.—*Injury Reactions and Healing in Various Skin Areas*

A

Injury Reactions After 24 Hours (10 Subjects)

	Upper Arm	Lower Arm	Back	Abdomen	Calf of Leg
Size of lesion (mm.)	5.3	5.1	5.3	5.5	5.2
S. e.	0.2	0.2	0.1	0.2	0.1
No. severe lesions	8	6	8	10	2

B

Injury Reactions After 10 Days (10 Subjects)

	Upper Arm	Lower Arm	Back	Abdomen	Calf of Leg
Size of lesion (mm.)	4.6	4.3	3.6	5.1	3.0
S. e.	0.1	0.2	0.1	0.2	0.2
No. severe lesions	2	2	0	5	0

C

Healing in 9 Days (10 Subjects)

	Upper Arm	Lower Arm	Back	Abdomen	Calf of Leg
Decrease of size of lesions (mm.)	0.7	0.8	2.7	0.4	2.3
% decrease of severe lesions	75	67	100	50	100

D

Injury Reactions Along the Leg After 24 Hours

Site of lesion	1	2	3	4
Size of lesion (mm.)	4.8	5.1	4.9	5.0
S. e.	0.3	0.1	0.2	0.2
No. severe lesions	0	2	11	5

E

Injury Reactions Along the Leg After 10 Days (20 Subjects)

Site of lesion	1	2	3	4
Size of lesion (mm.)	2.7	3.0	4.3	4.6
S. e.	0.1	0.1	0.3	0.2
No. severe lesions	0	0	11	4

F

Leg Injuries of 10 Patients on Bed Rest (24-Hour Reaction)

Site of lesion	1	2	3	4
Size of lesion (mm.)	4.3	5.2	5.3	5.0
S. e.	0.3	0.2	0.2	0.2
No. severe lesions	0	0	2	0

G

Leg Injuries of 10 Patients on Bed Rest (10-Day Reaction)

Site of lesion	1	2	3	4
Size of lesion (mm.)	2.0	2.5	2.7	2.6
S. e.	0.2	0.2	0.2	0.2
No. severe lesions	0	0	1	0

phery, but Site 3 still showed the most pronounced changes (Table 1E and Fig.). It is interesting to note that clinical ulcers are more likely to occur at the latter area. No significant difference in size was apparent between the third and fourth lesions or between the first and second. However, the two upper lesions were significantly smaller than the lower two. Healing, too, occurred more rapidly in the upper two.

2. Horton, B. T.; Sheard, C., and Roth, G. M.: Vasomotor Regulation of Temperatures of the Extremities in Health and Disease, J. M. Soc. New Jersey **37**:311-323, 1940.

To determine whether the upright position was an influence on this gradient of size of lesions along the leg, we repeated the experiments, using bedridden patients. The results showed the gradient in this series was less pronounced, and healing took place more rapidly (Table 1F and G).

FACTORS INFLUENCING INJURY REACTION AND HEALING

Site has an undeniable effect on injury, and this suggested an inquiry into the factors responsible. Surgical principles teach that movement retards healing, but we chose relatively stationary areas for study. We determined the threshold for skin flare, as an indication of vascular reactivity, but found no significant differences. The size and intensity of skin flare are nonreproducible factors and are, therefore,

Healing of leg lesions 10 days after injury.

not useful for evaluation of local differences in the injury reaction. Several factors possibly having an influence on the reaction to injury and the rate of healing appear in Table 2. None of them showed more than a partial correlationship to the injury reactions.

The most likely physiological factors influencing the reaction to injury and healing would seem to be cutaneous temperature and rate of blood flow. The effect on healing was investigated in a series of experiments on 10 bed patients. We produced injuries, in the same way as described above, at symmetrical places on both legs, and one hour later wrapped one leg in an electric pad to produce a skin temperature of 99 to 101 F. This procedure was maintained for three days. After 10 days the lesion on the control side was 2.4 mm., while that on the heated side was 1.8 mm. (Table 3A). With an ice bag (45 to 65 F. skin temperature) instead of the electric pad,

the size of the lesions was 2.6 mm. The difference in results between heated and control sides was significant, whereas that between the chilled and the bare leg was not.

To determine the effect of immediate heat and cold on the extent of an injury reaction we carried out the same procedures as in the last group, but placed the heated pad and the ice bag on the leg 10 minutes before producing the injury and left them in place for half an hour afterwards. Cold increased the energy necessary

TABLE 2.—*Relationship of Injury Reaction and Healing to Various Physiological Variables*

	Upper Arm	Lower Arm	Back	Abdomen	Calf of Leg
Size of lesion after 24 hr. (mm.)	5.3	5.1	5.3	5.5	5.2
No. severe lesions (24 hr.)	8	6	8	10	2
Healing in 9 days	0.7	0.8	2.7	0.4	2.3
% decrease of severe lesions	75	67	100	50	100
Skin thickness (mm.)	1.2	1.4	2.8	1.8	2.2
Skin temperature (C.)	32.9	30.0	33.6	34.2	32.2
Circulation index (Sheard*)	2.28	1.82	2.96	3.75	1.95
Pain points/cm.^{2} (Strughold†)	208	203	212	188	172
Pain pressure threshold (Strughold†)	0.29	0.32	0.47	0.54	0.70

* Sheard, C.: Temperature of Skin and Thermal Regulation of Body, in Glasser, O., Editor: Medical Physics, Chicago, Year Book Publishers, Inc.

† Strughold, H.: Über die Dichte und Schwellen der Schmerzpunkte, Ztschr. Biol. **80**:367-380, 1924.

TABLE 3.—*Effect of Heat and Cold on Healing in Ten Bed Patients*

A

Temperature Maintained for 3 Days Starting 1 Hour After Injury

	24-Hour Reaction		10-Day Reaction	
	Size of Lesion, Mm.	No. Severe Lesions	Size of Lesion, Mm.	No. Severe Lesions
Control	4.5	2	2.4	2
Cold (45-65 F.)	4.5	2	2.6	2
Heat (99-101 F.)	4.2	2	1.8	0

B

Temperature Maintained from 10 Minutes Before Until 30 Minutes After Injury

		24-Hour Reaction		10 Day Reaction	
	Energy, Ma.	Size of Lesion, Mm.	No. Severe Lesions	Size of Lesion, Mm.	No. Severe Lesions
Control	5.5	4.6	3	2.5	2
Cold (45-65 F.)	5.8	4.5	0	2.0	0
Heat (99-101 F.)	4.7	4.6	6	3.4	5

to reach the critical temperature and decreased the severity of reaction, while heat decreased the amount of energy necessary, but exaggerated the reactions (Table 3B).

In appraising the effects of blood flow as such on the extent of injury reaction we attempted to isolate this from the factor of tissue-blood content. The rate of blood flow determines how fast applied heat leaves a part, while blood content largely determines capacity to take up heat. For these experiments the arm was used. A pressure cuff with a pressure of 80 mm. Hg. causes congestion and increases its blood content. Contrariwise, raising the arm for a minute and then suddenly applying a cuff with a pressure of 200 mm. Hg. keeps the arm relatively bloodless. After

the cuff was kept inflated for three minutes, sudden release of its pressure brought about a passive hyperemia. Table 4 shows how these conditions influenced the extent of injury reactions.

The injection of 0.25 cc. of 1:1000 solution of epinephrine subcutaneously in the opposite arm caused blanching of the skin, indicating decreased cutaneous circulation while 0.01 mg. of histamine per kilogram of body weight caused reddening of the skin, indicating vasodilation and increased blood flow. The results (Table 4) indicate tissue-blood content had only minor effects on the injury reactions. In contrast, the role of blood flow was more important. Thus, with retarded flow lesions were milder and heat energy requirements were smaller, while hastening blood flow produced severer lesions and required more heat energy.

TABLE 4.—*Effect of Change in Blood Supply and Blood Flow on Injury Production (10 Subjects)*

		24-Hour Reaction		10-Day Reaction	
	Energy, Ma	Size of Lesion, Mm.	No. Severe Lesions	Size of Lesion, Mm.	No. Severe Lesions
Control	5.5	4.6	6	3.6	5
Venous congestion	5.1	4.5	5	3.4	5
Bloodless	4.9	4.5	5	3.1	4
Passive hyperemia	5.7	4.5	5	3.7	5
Epinephrine	5.3	4.5	4	3.3	2
Histamine	6.1	4.7	6	3.8	6

TABLE 5.—*Effect of Temperature and Blood Flow on Production of Injury*

Conditions During Production of Injury	Influence on Severity of Reaction	Heat Energy Necessary for Standard Injury Production
Heat	Increased	Decreased
Cold	Decreased	Increased
Increased blood flow	Increased	Increased
Decreased blood flow	Decreased	Decreased

COMMENT

In the application of heat to produce injury[3] we have two physical variables to consider: the heat energy applied and the skin temperatures attained. In these experiments we produced lesions by applying sufficient heat to produce a standard skin temperature indepedent of the energy necessary to obtain or maintain this skin temperature. Thus, we see from Table 4 that in the control an energy of 5.5 ma. was necessary to maintain the fixed temperature of 54.5 F. With venous congestion and stasis, less energy, 5.1 ma., was necessary to obtain the same temperature. If in this latter condition we fixed the energy at 5.5 ma., the temperature level rose to 55.8 F., and the resulting injury was larger (3.7 mm., instead of 3.4 mm.). This indicates that the results obtained are limited by the methods used.

The results show also that heat application decreases the energy requirement necessary to obtain the standard skin temperature, and increased blood flow

3. Bazett, H. C.; McGlone, G., and Brocklehurst, R. J.: The Temperatures in the Tissues Which Accompany Temperature Sensation, J. Physiol. **69**:88-112, 1930.

increases the energy. Heat and increased blood flow are very much interrelated, and the energy necessary to be used indicates the relative importance of one or the other in their effect on injury production. Cold and decreased blood flow have a corresponding effect, with cold raising the energy need and decreased blood flow lowering it (Table 5).

Previously we saw that heat applied at the time of producing the injury increased the severity of reaction, but heat applied later had a favorable influence on healing. On the other hand, cold decreased the injury reaction and delayed healing. In the investigation of the influence of blood flow on healing we studied only the first phase, i. e., the effect of increased and decreased blood flow during injury production and found the results paralleled the influence of applied heat. While we did not attempt to increase the blood flow during the healing period, because of technical difficulties, we may assume that it paralleled the heat effect, since heating generally produces vasodilation and cooling produces vasoconstriction, just as changes of blood flow cause a corresponding change of temperature.

SUMMARY AND CONCLUSIONS

Injury was produced with conduction heat over an area of 5 by 5 mm. at a temperature of 54.5 C. and for a time of one minute irrespective of the amount of energy needed.

The skin area chosen markedly influences the severity of injury reaction and the rate of healing.

Down the leg from knee to ankle there is a gradient of increasing retardation of healing. This does not occur significantly if the patient is resting in bed. Bed rest also reduces absolute healing time. Applying moderate heat when the injury is made exaggerates the injury reaction, while chilling moderates the reaction.

If heat is applied during the healing period, the healing time is shortened, while cold slows the rate of healing.

The effects of varying the blood supply and flow at the time of producing the injury paralleled those obtained with the induced temperature changes.

ISONIAZID (NYDRAZID) IN TREATMENT OF CUTANEOUS DISEASES

Cutaneous Tuberculosis, Leprosy, Sarcoidosis, and Miscellaneous Dermatoses

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DURING the past year, isonicotinic acid hydrazide (isoniazid) has been employed widely in the treatment of various types of systemic tuberculosis.[1] Because of the favorable nature of preliminary studies, a trial of the drug seemed warranted in the treatment of tuberculosis involving the skin. This report summarizes observations on 7 patients with lupus vulgaris, 2 with scrofuloderma, 11 with erythema induratum (Bazin's disease), and 3 with papulonecrotic tuberculid. Two patients are reported on in detail. Four patients with sarcoidosis and one with the so-called rosacea-like tuberculid have been included. Leprosy has many clinical, pathological, and immunological similarities to tuberculosis; accordingly, a trial of isoniazid in the treatment of this disease was deemed important. Seven patients with leprosy were treated, three with the lepromatous, three with the tuberculoid, and one with the indeterminate form of the disease. Finally, a group of patients with miscellaneous skin diseases, including eight with chronic discoid lupus erythematosus, were treated with isoniazid.

The Isoniazid (Nydrazid) used in this study was supplied by Dr. Harvey Blank, of the Squibb Institute for Medical Research.

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1. Robitzek, E. H.; Selikoff, I. J., and Ornstein, G. G.: Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid, Quart. Bull. Sea View Hosp. **13**:27 (Jan.) 1952. Robitzek, E. H., and Selikoff, I. J.: Hydrazine Derivatives of Isonicotinic Acid (Rimifon, Marsilid) in the Treatment of Active Progressive Caseous-Pneumonic Tuberculosis, Am. Rev. Tuberc. **65**:402 (April) 1952. Bosworth, D. M.; Wright, H. A., and Fielding, J. W.: Marsilid in the Treatment of Tuberculous Orthopedic Lesions, Quart. Bull. Sea View Hosp. **13**:52 (Jan.) 1952. Greenberger, M. E.; Greenberger, A. J.; Klein, M., and Turell, M.: Chemotherapy of Genitourinary Tuberculosis with Isonicotinic Acid Hydrazide, New York J. Med. **52**:1041 (April 15) 1952. Elmendorf, D. F., Jr.; Cawthon, W. U.; Muschenheim, C.; McDermott, W., and Clark, C. M.: Isonicotinic Acid Hydrazide ("Nydrazid") in the Treatment of Tuberculosis, Scientific Exhibit, 101st Annual Session of the American Medical Association, Chicago, June 9-13, 1952.

PERTINENT LITERATURE

While the present work was in progress, other investigators initiated similar studies. Grütz [2] employed isoniazid in four cases of lupus vulgaris, one of scrofuloderma, and one of erythema induratum. The dosage was from 5 to 10 mg. per kilogram a day, and administration was continued for three weeks to three months. "Satisfactory" improvement was reported in all cases. Obermayer, Wilson, and Smith [3] noted decided benefit in one and Goldberg and Simon [4] in two cases of lupus vulgaris. Cordero [5] used isoniazid in five cases of lupus vulgaris, two of scrofuloderma, two of tuberculosis cutis orificialis, and one of "multiple disseminated tuberculosis of the skin." Response to treatment was rapid, with healing of lesions between the fifth and eighth weeks of therapy. Two patients with lupus erythematosus and one with sarcoidosis were unaffected by the drug.

TABLE I.—*Over-All Summary of Treatment with Isoniazid*

Diagnosis	No. of Patients	Results of Treatment
Tuberculosis cutis		
Lupus vulgaris	7	Good
Scrofuloderma	2	Good
Tuberculid		
Erythema induratum (2 with papulonecrotic tuberculid)	11	Poor in 9; good in 2
Papulonecrotic tuberculid	3	Good in 2; poor in 1
Rosacea-like tuberculid	1	Moderate improvement
Sarcoidosis	4	Poor
Leprosy		
Lepromatous	3	Moderate improvement
Indeterminate	1	Moderate improvement
Tuberculoid	3	Poor
Discoid lupus erythematosus		
Localized	7	Poor
Disseminate	1	Poor
Dermatitis herpetiformis	3	Poor
Benign familial pemphigus	1	Poor
Hidradenitis suppurativa	1	Good
Acrosclerosis	1	Poor

A single study on the use of isoniazid (Nydrazid) in leprosy has been reported by Latapi and his associates.[6] Thirteen patients with lepromatous and one with tuberculoid leprosy were treated with the drug in a daily dosage of 3 to 5 mg. per kilogram for seven to nine months. Distinct, although slow, improvement was noted in all patients with lepromatous leprosy. Lesions flattened; no new ones developed, and demonstrable leprosy bacilli became greatly decreased in numbers. There was no effect on the one patient with tuberculoid leprosy.

2. Grütz, O.: Vorläufiger Bericht über die Wirkung des Neoteben (Isonikotinsäurehydrazid) auf die Hauttuberkulose, München. med. Wchnschr. **94**:1298 (June 27) 1952.

3. Obermayer, M. E.; Wilson, J. W., and Smith, P. N.: Isonicotinylhydrazine (Rimifon®) in the Treatment of Lupus Vulgaris: Report of a Case, J. Invest. Dermat. **19**:311 (Nov.) 1952.

4. Goldberg, L. C., and Simon, C. R.: Treatment of Lupus Vulgaris with Isoniazid: Report of 2 Cases, J. A. M. A. **151**:640 (Feb. 21) 1953.

5. Cordero, F. A.: Tuberculosis of the Skin Treated with Isonicotinic Acid Hydrazide, The Schoch Letter, from the Penicillin Research Center, Southwestern Medical Foundation, Dallas, Texas, Feb., 1953.

6. Latapi, F.; Rubio, J. B.; Rodriguez, O., and Estrada, C. E.: Report on 9 Months' Treatment of Leprosy with Isoniazid (Nydrazid), J. Invest. Dermat., to be published.

Fig. 1 (Case 1).—*A*, lesions of lupus vulgaris after therapy with calciferol, paraaminosalicylic acid, and streptomycin. *B*, appearance after six months of therapy with isoniazid.

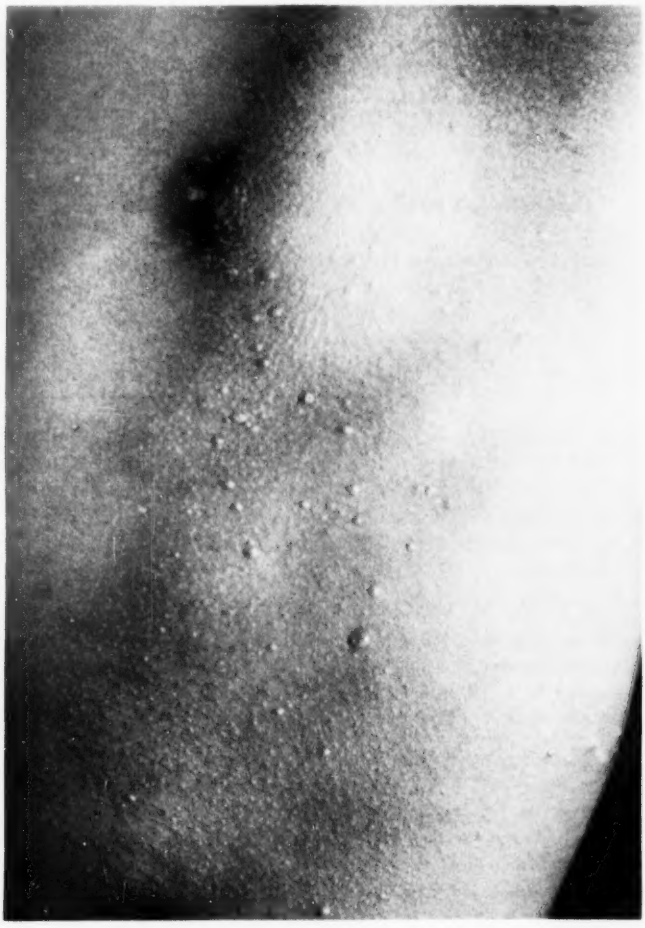

Fig. 2 (Case 2).—Hypertrophic papular lesions on the torso resulting from small papulonecrotic tuberculid lesions, which healed after isoniazid therapy.

METHOD OF PRESENT STUDY

All patients were subjected to a thorough preliminary evaluation; this included a general physical examination, biopsy, and, when indicated, a roentgenogram of the chest, quantitative tuberculin tests, smears and cultures, sputum examinations,

Fig. 3 (Case 2).—Vaccination-like scars following large papulonecrotic lesions on the left elbow, which healed after therapy with isoniazid, 100 mg. three times a day.

blood cell counts, and urinalyses. The daily dose of isoniazid varied; initially, it was kept low (3 mg. per kilogram or 0.2 gm.). Later on, this dose was increased, in some instances to 1.2 gm. daily.

The distribution, number of patients treated, and the over-all effect of isoniazid therapy are shown in Table 1.

REPORT OF CASES

CASE 1.[7]—F. O., a white man aged 53, had always been in good general health. There was no known exposure to tuberculosis. The present condition began as a small patch on the vertex of the scalp in early childhood. At age 6, left posterior cervical adenopathy developed, and skin lesions soon appeared in the overlying area. The process spread gradually over the back and the left side of neck and to the lobule of the left ear. The right side of the neck had become involved two years earlier.

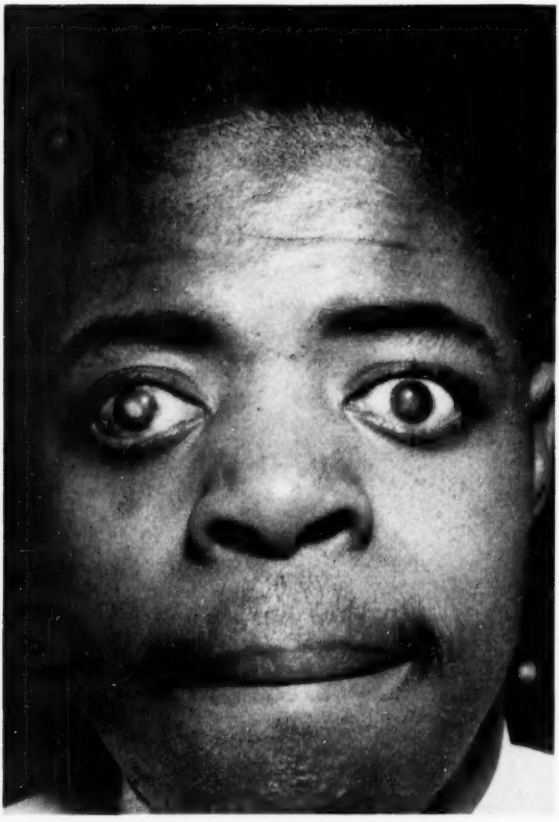

Fig. 4 (Case 2).—Tuberculous keratitis arrested by isoniazid therapy. Note varioliform scars between eyebrows and hypertrophic scars of chin resulting from papulonecrotic lesions.

The patient was first seen in January, 1952, at which time typical lupus vulgaris was present in the areas mentioned. The involved skin was diffusely red, with many apple-jelly nodules. A roentgenogram of the chest showed old pleurisy but no evidence of active tuberculosis. The tuberculin test was positive with a 1 : 100,000 dilution, and biopsy disclosed changes characteristic of lupus vulgaris. Therapy was initiated with calciferol, 50,000 units of vitamin D daily for 2 months; paraaminosalicylic acid for 3 weeks, and streptomycin, 1 gm. daily for 3 weeks in a first course and for 12 days in a second. Moderate improvement ensued. The appearance of the lesions at this time is shown in Figure 1*A*.

7. The patient was a private patient of Dr. Charles Sheard, who allowed his case to be reported in this study.

Isoniazid therapy, 200 mg. daily, was begun on May 1 and continued for six months. There were no adverse reactions to therapy. The lesions involuted slowly and were practically gone by Sept. 1 (Fig. 1*B*).

CASE 2.—V. J., a 16-year-old Negro boy, had generalized tuberculosis following measles in 1940. On his admission to Bellevue Hospital, a roentgenogram of the lungs disclosed consolidation at the right base. There was mottling of the inner half of the left lung field, with a dense rounded shadow to the right of the mediastinal shadow. The Mantoux test was strongly positive, and biopsy of enlarged cervical nodes showed tuberculosis. Bilateral exophthalmos and lumbar scoliosis were present. The sputum was negative for tubercle bacilli on smear and culture.

He was a patient at Sea View Hospital from April, 1941, to November, 1944. At this time, his condition was complicated by deformity of elbow and wrist epiphyses. A roentgenogram taken on admission showed dense hilar shadows from the left superior mediastinum to the clavicle; hilar markings were exaggerated. Phlyctenular conjunctivitis developed in November, 1941, and resulted in scarring, with loss of vision in the right eye and partial loss of vision in the left eye. The following February, papulonecrotic tuberculids appeared on the elbows and knees; in June, 1942, a subglottic edema necessitated tracheotomy.

The patient was rehospitalized at Bellevue from September, 1946, to May, 1947. The tuberculous conjunctivitis was still present, and keratitis had developed. A lung roentgenogram showed root fibrosis, a large circumscribed fibrotic nodule at the left base, and bronchiectatic changes in both bases. Scrofuloderma, with tonsillar and adenoidal enlargement, was noted in March, 1947. On removal of the tonsils and adenoids tuberculosis of these tissues was demonstrated. Calcification, probably tuberculous, of the left kidney was identified in 1949. On discharge, x-ray studies disclosed only basilar pulmonary fibrosis.

Erythematous, scaly papules and deep nodules developed over the extremities, trunk, and face in February, 1950. Minimal improvement was obtained by prolonged therapy with streptomycin and paraaminosalicylic acid. On examination in May, 1952, active skin lesions were present, the cervical lymph nodes were enlarged, and there was a tenosynovitis of the left wrist. Evidence of active keratitis was demonstrated. Isoniazid therapy, 0.3 gm. daily, was instituted and continued without reaction for six months. While the patient was undergoing therapy, the cervical nodes involuted, the cutaneous papules and deep "gummatous-like" nodules disappeared, and the tenosynovitis underwent objective and subjective improvement. The end-results of treatment are shown in Figures 2, 3, and 4.

RESULTS OF TREATMENT IN CUTANEOUS TUBERCULOSIS

The effect of isoniazid on frank tuberculosis of the skin is shown in Table 2.

There were seven patients with lupus vulgaris, which varied in duration from 5 to 50 years. Four were treated with 0.2 gm. of isoniazid daily, one with 0.4 gm., one with 0.6 gm., and the last with 1.2 gm. The duration of treatment at the time of the report varied from three to six months. The response to treatment was uniformly good, and improvement is continuing with maintenance therapy. There was no evidence that improvement was more rapid or more pronounced with the heavier dosage schedules. One patient experienced an erysipelatous type of exacerbation (Herxheimer type of reaction?) 10 days after the onset of therapy, but treatment was continued and the reaction subsided in four days.

Two patients had scrofuloderma. One, with a single sinus tract, had complete healing in 75 days on a dosage of 0.2 to 0.3 gm. of isoniazid daily. The second patient, who had Pott's disease, had draining parasternal sinuses, which healed completely after two months of therapy with 0.6 to 0.9 gm. of isoniazid daily.

There were 11 patients with erythema induratum, which varied in duration from 8 months to 12 years. Two of these had lesions of papulonecrotic tuberculid as well. All this group were women, and seven were in the fifth decade of life. In general, the response to therapy was poor. The dose varied from 0.2 to 0.5 gm. of

isoniazid daily, the duration of treatment being 56 to 85 days. In two patients healing was accelerated and was complete in three months. New lesions developed in five patients during therapy and in a sixth patient after therapy was terminated. In one of these, a concomitant cervical and axillary tuberculosis subsided during therapy.

The lesions of papulonecrotic tuberculid, as they coexisted with those of erythema induratum, were uninfluenced by isoniazid. Two patients with papulonecrotic tuberculid responded well to therapy. The first patient had severe chronic systemic tuberculosis (Case 2), while the second, with acnitis, had continuous lesions for some 20 years prior to isoniazid therapy. A third patient with papulonecrotic tuberculid experienced no improvement, and new lesions continued to develop during 90 days of therapy at a 0.2-gm. daily level. One patient was thought to have rosacea-like tuberculid. Although the tuberculous nature of this entity is

TABLE 2.—*Pertinent Data and Results of Treatment in Cutaneous Tuberculosis*

Diagnosis	Age	Sex	Daily Dose, Gm.	Duration of Therapy, Days	Degree of Healing	Untoward Reactions	Additional Data
Lupus vulgaris	58	M	0.2	120	Nearly complete	None	Glandular tuberculosis at age 6
Lupus vulgaris	66	M	0.2	90	Nearly complete	None	Recurrent lesions, 38 years
Lupus vulgaris	51	F	0.6 to 1.2	180	Nearly complete	Headache, nausea	Previous improvement with vitamin D_2
Lupus vulgaris	49	M	0.3 to 0.6	180	Complete	None	Previous therapy, including use of vitamin D_2, unsuccessful
Lupus vulgaris	53	F	0.4	90	Moderate	None	Improvement slow but consistent
Lupus vulgaris	50	F	0.2 to 0.3	75	Nearly complete	None	.....
Lupus vulgaris	45	M	0.2 to 0.4	46	Moderate	Urticaria	Urticaria after 1 month; therapy stopped for 10 days, then resumed without reaction at 50 increasing to 200 mg.
Scrofuloderma	39	M	0.2 to 0.3	186	Complete (75 days)	None	Cultures and guinea pig inoculation, positive
Scrofuloderma	46	F	0.6 to 0.9	90	Patient cured; sinus tracts closed in 2 months	Headache, vomiting, facial paresthesia	Pott's disease; reactions subsided when dosage was reduced to 0.3 gm. daily

in doubt, in the patient in question intercurrent tuberculous pleurisy with effusion developed. Moderate improvement was noted after one month of isoniazid therapy. The generally poor results in the tuberculid group are noteworthy. However, the spectacular response of 4 patients to therapy suggests that the tubercle bacilli were in walled-off foci in the remaining 10 patients. An effective therapeutic dose of isoniazid would not reach the organisms in such foci. The possibility of developing resistance to isoniazid could not be confirmed because of the absence of available organisms for testing.

THERAPY OF LEPROSY WITH ISONIAZID

Seven patients with leprosy were treated with isoniazid. The known duration of the disease varied between 5 and 40 years. Of the patients, three had the lepromatous, one the indeterminate, and three the tuberculoid type. Pertinent data and the response to isoniazid therapy are detailed in Table 3.

In the first patient with lepromatous leprosy, isoniazid, in a dose of 0.2 to 0.4 gm. daily for eight months, resulted in transient initial improvement, followed by a par-

tial clinical relapse. The lesions became bacteriologically negative after four months of treatment, and improvement has been maintained to date. Moderate improvement of lesions was noted in the last two patients with lepromatous leprosy. One patient with indeterminate leprosy improved greatly during six months of treatment. None of the three patients with tuberculoid leprosy was improved by isoniazid therapy; in one, a leprous reaction occurred in the first month of therapy, and subsequently new lesions continued to occur.

RESULTS OF ISONIAZID THERAPY IN MISCELLANEOUS CONDITIONS

Four patients with sarcoidosis were treated with isoniazid in a dosage of 0.2 to 0.5 gm. daily for two to five months. Two of the patients had lymphadenitis and one pulmonary sarcoid. The adenitis subsided temporarily in one patient, but there was no improvement in the cutaneous lesions in any of the four patients.

TABLE 3.—*Pertinent Data and Results of Treatment in Leprosy*

Type of Leprosy	Age	Sex	Daily Dosage, Gm.	Duration of Therapy, Days	Degree of Improvement	Untoward Reactions	Additional Data
Lepromatous	23	M	0.2 to 0.4	238	Moderate	Leprous reaction prior to therapy, treated with cortisone	Initial flattening of lesions; partial clinical relapse, then steady improvement
Lepromatous	28	F	0.6	180	Moderate	Dizziness, occasional nausea	Nodular lesions involuted; increase in weight
Lepromatous	19	M	0.3 to 0.9	90	Moderate	None	Partial involution of nodules and infiltrated plaques
Indeterminate	55	F	0.3 to 1.2	180	Excellent	Dizziness, occasional nausea	Disappearance of all nodules and plaques; patient felt better than in years
Tuberculoid	60	M	0.6 to 0.9	180	None	Nausea	.....
Tuberculoid	29	F	0.3 to 0.6	150	None	None	Previous nephrectomy for tuberculous kidney; cutaneous lesions generalized
Tuberculoid	34	F	0.3 to 0.4	120	Progression, first month of therapy	Leprous reaction during therapy	Eruption previously stationary for years; new lesions developed and old ones became aggravated

Chronic discoid lupus erythematosus was present in eight patients. The duration of the disease varied from 4 to 25 years. Isoniazid in doses of 0.2 to 0.6 gm. daily was given for periods up to five months. No improvement was noted. One patient had the generalized discoid form of the disease, with borderline evidence of subacute lupus erythematosus. Therapy was initiated with 0.6 gm. of isoniazid daily. After 14 weeks of therapy, laboratory and clinical evidence of acute disseminated lupus erythematosus, with identification of L. E. cells, appeared. It is a matter of conjecture whether or not the exacerbation and progression were related to the administration of the drug.

Because of the alleged value of nicotinic acid in some cases of dermatitis herpetiformis, isoniazid was given a trial in three cases of this disease. Doses varied from 0.3 to 0.4 gm. daily. Treatment was continued for three to eight weeks, but improvement did not occur.

Isoniazid therapy was without benefit in one case of generalized benign familial pemphigus (Hailey-Hailey disease) and in one of acrosclerosis. The drug was used in a dose of 0.3 gm. daily for one month in a single case of hidradenitis suppurativa; there was marked improvement, which is continuing with additional therapy.

UNTOWARD REACTIONS TO ISONIAZID

Reactions were not noted in patients treated with 0.2 gm. of isoniazid daily. In one patient urticaria, dizziness, and loss of coordination developed after administration of 0.3 gm. of the drug daily for four weeks. The symptoms disappeared rapidly after withdrawal and did not recur when the drug was administered again in a dose of 0.05 to 0.2 gm. daily in conjunction with antihistamine therapy. Urticaria was noted in a patient receiving 0.4 gm. of isoniazid daily. After a rest of two weeks, 0.2 gm. of the drug given daily (with simultaneous antihistamine therapy) was well tolerated. Nausea was experienced by seven patients. It occurred in conjunction with severe headache in one; with vomiting, severe headache, and facial paresthesias in a second, and with dizziness in three others. Dosage levels in this group varied from 0.3 to 1.2 gm. daily. Therapy was tolerated without reaction when the dose was reduced, in one case from 0.4 to 0.3 gm., in three from 0.9 to 0.6 gm., and in two from 1.2 to 0.6 gm. Reduction of dose was not necessary for one patient. One patient noted transitory tingling of the lower extremities during therapy; this subsided with continued treatment. As stated, a transient Herxheimer-like exacerbation was noted in one patient with lupus vulgaris, an acute leprous reaction in a patient with tuberculoid leprosy, and a transformation of chronic disseminated lupus erythematosus into the acute form of the disease in one patient; of these reactions, only the Herxheimer-like erysipelatous exacerbation of lupus vulgaris could be attributed to isoniazid therapy. In no instance was discontinuance of therapy necessary because of untoward reactivity.

SUMMARY

Tuberculosis of the skin in 9 cases; tuberculid, in 15; leprosy, in 7; sarcoid, in 4, and miscellaneous conditions, in 14, were treated with isoniazid (Nydrazid).

The drug had a decidedly beneficial effect in all nine cases of lupus vulgaris and scrofuloderma.

The response of tuberculid to therapy was poor in 11 cases, excellent in 3, and satisfactory in 1.

In three cases of lepromatous and one of indeterminate leprosy the disease responded satisfactorily after three to four months of continuous therapy.[8] There was no response to isoniazid in three cases of tuberculoid leprosy.

The drug was not of benefit in four cases of sarcoid, three of dermatitis herpetiformis (Duhring's disease), 7 of chronic discoid, and one of chronic disseminated lupus erythematosus.

Doses of 0.2 to 0.6 gm. daily were well tolerated. Reactions were somewhat troublesome when daily doses of 0.8 to 1.2 gm. were given, but there was not a single severe toxic reaction.

There was no definite evidence that daily doses of 0.8 to 1.2 gm. of isoniazid were superior to the smaller doses.

8. An additional (fourth) case of lepromatous leprosy has been treated with isoniazid 0.4 gm. daily for six months. This therapy combined with four short courses of sulfoxone (Diasone) has resulted in marked clinical improvement.

INFLUENCE OF PRESSURE ON NODULES OF XANTHOMA TUBEROSUM

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IT IS A PRINCIPLE of pathology that intermittent pressure produces hypertrophy and constant pressure atrophy. The application of pressure bandages to the nodules of xanthoma tuberosum will gradually bring about their regression. On the other hand, prolonged passive congestion may lead, under certain circumstances, to the development of new xanthomatous nodules.

CASE REPORTS

CASE 1.—M. F. B., a white man of 46, who is the proprietor of a gasoline service station, first consulted me on March 7, 1950. He stated that his skin trouble had begun in the fall of 1943. A low-fat diet, insulin, and dried thyroid gland had failed to produce any material change in his condition. No other member of his family had similar skin changes; since his relatives lived in scattered parts of the United States, they were not available for examination.

The patient's skin exhibited yellow, orange, and slightly violaceous round nodules and mushroom-like masses from 1.0 mm. to 2.5 cm. in diameter, symmetrically distributed on the extensor surfaces of the elbows and knees, buttocks, hips, axillary folds, dorsal surface of the fingers, and ulnar edges of the hands. Yellow ribbon-like infiltrations were present in the creases of the palms and fingers, although the uninvolved portions of the palms had a normal color. The oral mucosa and general physical examination revealed essentially normal findings. In short, clinically, the patient presented a classic case of xanthoma tuberosum.

The routine blood and urine studies showed results which were within normal limits. Significant changes were found in the study of the fatty elements of the blood as follows: total cholesterol, 700 mg.; cholesterol esters, 490 mg.; phospholipid, 455 mg.; triglyceride, 912 mg., and total lipid, 2,067 mg. per 100 cc.

The patient was given detailed instruction in regard to a low-fat and low-calorie diet. During the next 18 months, he received ultraviolet light, vitamin A orally and parenterally, desiccated thyroid gland, dextrorotary amphetamine sulfate, and lipotropic substances in the generally accepted doses. During this interval, his weight remained relatively stationary, approximately 183 lb. (83 kg.). The xanthoma tuberosum lesions did not change materially during this time.

On the occasion of his visit to my office on Sept. 13, 1951, the patient proudly exhibited his hands and remarked that hard work agreed with him. True enough, the yellow bands had disappeared from the creases of the palms, although characteristic yellowish nodules remained on the dorsal surfaces of the fingers and the ulnar edges of the hands. He explained that he had been recently doing considerable manual labor involving the use of a pick, shovel, and pipe wrench. His enthusiasm was so great and the physical changes so striking that his observation could not be ignored.

On that day, he exhibited many nodular lesions on the anterior aspects of the knees (Fig. 1). It was decided to study the effect of continued pressure on the nodules on the left knee, using those on the right knee as controls. A pressure dressing made of elastic adhesive bandage (Elastoplast) was immediately applied and renewed at weekly intervals thereafter. While the lesions

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began to melt away, the small ones disappeared entirely. On Jan. 24, 1952, disc-like pieces of rubber cut from truck tire, inner tubes were placed over the remaining tumors, which were then covered by means of elastic adhesive bandages. As the size of the lesions decreased, the rate of progress became slower.

By midsummer of 1952, several soft-elevated lesions remained on the anterior aspect of the left knee (Fig. 2). Since these were not influenced by additional pressure bandages, it was surmised that, perhaps, the xanthomatous elements had disappeared, leaving fibrous scar tissue. Because the patient was becoming anxious to apply pressure bandages to the right knee and since maximum improvement presumably had occurred, a piece of tissue was removed from the largest remaining lesion.

Histologic examination (Dr. Fred D. Weidman) revealed that, for a position like that of the knee, the epidermis was slightly thickened. In the corium, a few of the collagenous bundles stood out because they were larger than the others. Some were rather shreddy and doubtless reflected the dissection and expansion to which they had been subjected on the part of the lipoidal processes. At certain places, a few collapsed hyperplastic capillaries remained, as around hair follicles. Xanthoma cells were not discovered.

Fig. 1 (Case 1).—Nodules of xanthoma tuberosum on the knees, Sept. 13, 1951.

Case 2.—F. B. J., a white man of 39, who is the proprietor of a small restaurant, had had xanthoma tuberosum since the summer of 1946. Large doses of vitamin A, dried thyroid gland, ultraviolet light, lipotropic substances, and a low-fat high-carbohydrate diet with insulin were ineffective in controlling his disease. Earlier blood-sugar determinations had varied from 83 to 105 mg. per 100 cc., while two estimations of total cholesterol had been 560 and 345 mg. per 100 cc., respectively.

Examination revealed many chamois-colored papules in the creases of the palms and fingers and larger yellowish nodules on the extensor surfaces of the elbows. Only a few small lesions were present in the patellar regions, but innumerable small rounded papules were present on the buttocks. Many of the lesions in this region were pierced by a hair. In addition to the striking follicular character of the lesions on the buttocks, another outstanding feature in this case was the presence of a few tiny shot-like xanthomatous papules on the outer surfaces of the ears. In one place on the middle of the right helix, they were grouped into a mulberry-like mass. The oral mucosa and general physical condition were essentially normal.

The routine urine and blood studies were within normal limits. The fatty elements of the blood were as follows: total cholesterol, 1,010 mg.; cholesterol esters, 645 mg.; phospholipid, 675 mg.; triglyceride, 2,677 mg., and total lipid, 4,362 mg. per 100 cc.

Because the greatest concentration of lesions was on the elbows, it was decided to apply pressure bandages to one of them, using the other as a control. Accordingly, on Sept. 25, 1952, an elastic adhesive bandage was applied snugly to the right elbow. As a rule, the dressing was changed at weekly intervals, although the patient would occasionally wear a bandage for a longer time. On several visits, the patient complained of swelling of the hand and forearm below the bandage. He was advised to continue on a low-fat diet and to take vitamin A and small doses of thyroid orally.

During the weeks that followed, lesions on the extensor surface of the bandaged elbow showed a gradual diminution in size. At the same time, there was no perceptible change in the lesions on other portions of the body. Early in December, I began to suspect that new nodules were appearing on the right hand below the pressure bandage. The process on the left hand and elsewhere seemed stationary. Examinations during the remainder of December and early January confirmed my suspicions. Finally, on Jan. 20, 1953, the patient complained that although the bandage was reducing the lesions on the elbow, it was causing them to appear on the palms and

Fig. 2 (Case 1).—Constant pressure by means of elastic adhesive bandages has brought about regression of the nodules of xanthoma tuberosum on the left knee, Oct. 9, 1952.

fingers. He also agreed that new lesions had not been appearing on the left hand or other portions of the body. At that time, the nodules on the treated elbow were about two-thirds their former size.

COMMENT

One can only speculate as to the mechanism involved with the use of pressure dressings in the regression of the nodules of xanthoma tuberosum. Undoubtedly, pressure causes compression of the capillaries and small vessels, leading to reduced circulation and interference with the normal metabolic processes. The xanthoma cell, no longer imbibing serum overloaded with lipid, either consumes its lipoidal contents or casts them back into the circulation so that, histologically, only fibrosis remains. If, perhaps, histologic sections could be taken at intervals as the nodules undergo involution under pressure, the results observed would have significance in the understanding of the pathogenesis of xanthoma. Apparently, there must be a free circulation of tissue juices for the lipoidal substances to be deposited in the cells.

While interference with the arterial supply leads to a regression of xanthomatous nodules, partial obstruction of the venous and lymphatic circulation seems to favor the deposition of cholesterol in the cells. It is reasonable to assume that there was increased venous pressure in the right hand and forearm in Case 2, since the patient experienced swelling of the parts, particularly when the hands were dependent and at rest. The presence of lipid-laden serum under conditions of passive congestion apparently enables the individual cells to imbibe more freely of the fatty contents of the serum. Anatomical differences and the wearing of shoes probably prevented congestion of the leg and foot on the treated side in Case 1.

From a practical clinical viewpoint, pressure dressings will afford relief to those persons who, in the course of their daily activities, frequently injure the nodules on the elbows and knees, with superficial ulceration and crusting sometimes occurring. Of course, it remains to be seen whether deposits of lipids will occur once again in the tissue cells when the pressure has been discontinued.

SUMMARY

Constant pressure applied by means of elastic adhesive bandages (Elastoplast) for about one year brought about the regression of the nodules of xanthoma tuberosum. The soft remnants of the tumors remaining at the end of that time were found histologically to be composed of fibrous tissue, with no xanthoma cells discoverable.

Prolonged passive congestion of an extremity produced by means of a circular bandage seems to favor the deposition of lipoidal substances and the formation of xanthomatous nodules.

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INFLUENCE OF X-RAY CONES ON THE DOSE

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X-RAY CONES are used in superficial therapy as handy means of limiting the field of irradiation. It is known that cones may affect the dose in comparison to that delivered without cone under otherwise identical circumstances. The literature on this subject appears scant. Some years ago one of us had shown how cones used for deep x-ray therapy reduced the dose.[1] Recently, Raventos and Schwarz [2] have called attention to the fact that the field, delimited by the lead diaphragm of the cone, is not of uniform intensity.

Measurements on a modern x-ray machine for superficial therapy showed variations of the dose with and without cone. As the differences under certain circumstances were considerable, the results are herewith presented.

MATERIALS AND METHODS

The measurements were carried out on three Picker-Waite Zephyr units. Commercial cones of different field sizes were used—2.0, 2.5, 2.8, 7.5, 10, and 15 cm., respectively. The cones consist essentially of two parts: the diaphragm, a metal plate at the top, with a central opening, the aperture, which limits the x-ray beam of the tube, and the cone proper. There were differences of aperture and construction in cones for different field sizes and also among cones of apparently the same size. These differences are shown in the Chart and the Table. The factors were 80 kv. and 4 and 5 ma. respectively. No filter was used. The focus-skin distance was usually 20 cm.; for certain measurements it was increased up to 55 cm. By means of a fluoroscopic screen we made certain that the x-ray field fully covered the chamber of the measuring Victoreen instrument; the dimensions of the chamber were about 1.2 by 2.3 cm. The measured r figures were transformed into relative values; the dose measured when no cone or other attachment to the tube was used was considered 100%. The figures are composites of repeated measurements.

RESULTS

The results are not uniform. Theoretically there are three possibilities: 1. The cone does not materially alter the dose. 2. The cone decreases the dose. 3. The cone increases the dose. All three possibilities materialized. As the Table and the Chart show, we are dealing mainly with two variables: diameter of the distal end of the cone and diameter of the aperture (the opening of the diaphragm). As has been

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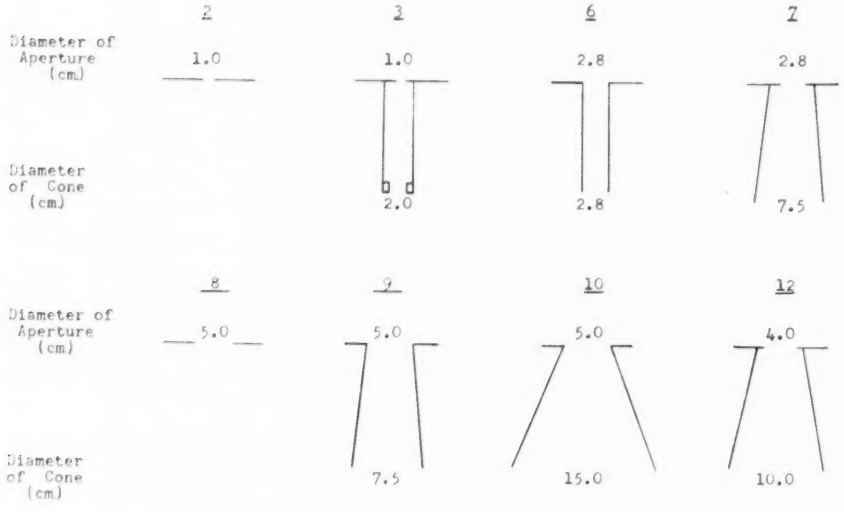
1. Epstein, S.: Der Einfluss des Tubus auf die Dosis, Strahlentherapie **40**:493-507, 1931.

2. Raventos, A., and Schwarz, G. S.: Penumbra Effect in Therapy Cones, Radiology **56**:84-88 (Jan.) 1951.

SCHEMATIC DRAWINGS OF CONES AND DIAPHRAGMS USED*



* The numbers correspond to those of the Table. The diameter of the diaphragm was always 10 cm.

Influence of Cones and Diaphragms on the Relative Dose

Case	Cone: Diameter of Aperture of Diaphragm, Cm.	Cone: Diameter of Open End of Cone, Cm.	Dose * (Measured at Various Distances): 1 20 Cm. %	2 25 Cm. %	3 31 Cm. %	4 40 Cm. %	5 55 Cm. %
1	No diaphragm	No cone	100	100	100	100	100
2	1.0	No cone	88	85	84	...	...
3	1.0	2.0	(†)	84	83	78	78
4	2.5	No cone	97	...	...	...	...
5	2.5	2.5	102	92	92	86	...
6	2.8	2.8	99	95	93	88	85
7	2.8	7.5	102	...	...	...	...
8	5.0	No cone	98	...	...	...	...
9	5.0	7.5	108	99	102	96	90
10	5.0	15.0	98	99	...	...	98
11	4.0	No cone	98	...	...	...	...
12	4.0	10.0	99	...	...	...	...

* The dose is expressed as the percentage of that measured without cone or diaphragm. The latter is considered 100% for each distance.

† Field too small for measuring chamber.

shown previously,[1] the size of the aperture limits to some extent the amount of radiation delivered. This is so because the radiation originates not only from the center of the anode, but also from other parts of and from behind the anode. This additional radiation comes off at a different angle, and therefore part of it is absorbed by the diaphragm.

The effect of the size of the aperture is demonstrated in the Table. The 10-mm. aperture (Case 2) reduces the dose to 88%, whereas the 25-mm. (Case 4) and larger apertures did not appear to influence the delivered dose appreciably.

Interesting and unexpected was the result in Case 9. Repeated measurements demonstrated an average increase of about 8% for the 7.5-cm. cone with a large aperture (5.0 cm.). A similar increase of the dose was observed for the 7.5-cm. cone with a smaller aperture (2.8 cm.) (Case 7, Table). Although the dose here was only 102% of that without a cone, a comparison must be made between this value and that (Case 4) where the dose through a smaller base plate alone was measured. Such a comparison indicates that the 7.5 cm. cone caused an increase of about 5%. To what factor this is due, we cannot state with certainty, but it seems suggestive to us that the increase of the dose is due to secondary radiation from the wall of the cone. This assumption is supported by measurements at different distances, as shown in columns 2 to 5 of the Table. An increase of the dose (Cases 5, 7, and 9) was found only when the measuring chamber was directly below the cone, at the 20-cm. distance. For several reasons one would expect less effect, or none at all, from the secondary radiation when the measuring chamber was farther removed from the cone.

No influence upon the dose was noted when a large cone of 15 cm. (Case 10) was used. It is evident that far less radiation hits the wall of this cone than that of the smaller ones, and therefore less secondary radiation is to be expected. In this instance there was no change of the comparative dose at different distances.

COMMENT

Before any conclusions are drawn, several limitations of this study must be mentioned. The measurements were made only at the center of the field; the size of the measuring chamber was too large for dependable measurements of the 2.0-cm. cone at 20-cm. distance. If secondary radiation from the wall of the smaller cones is a factor—as it seems from Case 5 in the Table—one cannot accurately determine the dose delivered through the smaller cones by measurements at a greater distance. There were differences between individual measurements, although the general trend was always in the same direction. For these and other reasons (e. g., role of back-scattering) the figures of the Table should be considered as expression of a trend rather than as representations of exact figures.

Even so, it seems that the results of our measurements are of more than theoretical interest. The use of one small cone (cf., Cases 2 and 3) reduced the dose by about 12%. As this cone is used for treatment of epitheliomas, that means that in cases in which a dose of 5,000 r was intended only about 4,400 r was actually given, provided one was guided by the values measured without a cone. This is a considerable discrepancy which cannot be ignored in the treatment of a malignant lesion of the skin or lip.

As far as the larger cones are concerned, the practical effects are not significant. With the exception of Case 9, the actual dose was about the same with cone and

without cone. Even in Case 9 (Table), in which the dose was increased by about 8%, this is of minor importance, because this cone is used almost exclusively for the relatively small doses employed in treating inflammatory dermatologic conditions.

Although the studies were made on only one model of superficial x-ray machines, similar conditions may exist in other brands. If our results can be confirmed, they suggest that the manufacturers construct and standardize their cones in such a way that there will be no difference in the dosage whether a cone is used or not.[3]

In the meantime, it is recommended that the users of superficial x-ray equipment have the output of their machines measured with and without cones.

SUMMARY AND CONCLUSIONS

The following conclusions were reached:

The use of a cone on superficial x-ray machines influences the actual dose.

The dose given through a cone may be identical, smaller, or larger in comparison with that without cone. An explanation of these phenomena is suggested.

Under certain circumstances the actual dose given through a cone appears to be considerably less, namely, 12%.

The implications of these findings are discussed. It is suggested that the manufacturers consider this influence of the cone and so construct cones to eliminate these variations.

It is also suggested that the users of such equipment have their machines measured with and without cones in order to make sure which dose is delivered to the patient.

3. The Picker X-Ray Corporation (Schiving, R. C.: Personal communication to the author) is aware of the problem. They had conducted similar experiments on their deep-therapy equipment, and, generally speaking, their results were comparable. Therefore, it can be assumed that the manufacturer will take care of this matter; it seems likely that this point has already been taken into consideration in the construction of new cones. Even so, many dermatologists and radiologists are still using cones of older construction.

LOW INCIDENCE OF DERMOGRAPHISM IN SUBACUTE AND CHRONIC URTICARIA

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DERMOGRAPHISM is a term applied to wheals of various sizes and shapes produced on the skin by local physical or mechanical irritation, such as stroking, scratching, rubbing, and pinching. Synonomous terms are factitious urticaria (urticaria factitia), dermographic urticaria, autographism, mechanical urticaria, and dermographia. Dermographism is to be distinguished from "pressure" urticaria.[1] Dermographism is provoked within a few minutes by a relatively gentle superficial mechanical influence, such as stroking of the skin. Pressure urticaria appears only after a latent period varying from 2 to 24 hours and only at the sites of relatively great and persistent pressure, such as the soles, palms, and buttocks.

Our interest in the relationship between dermographism and subacute or chronic urticaria was aroused when we noted many patients with dermographism were being referred for skin testing to the Allergy Section under the diagnosis of "chronic urticaria." On investigating the literature, we found marked differences of opinion as to the relationship of these entities. Walzer[2] stated that dermographism is a frequent accompaniment of urticaria. He tested for dermographism 48 patients without urticaria taken at random from the general run of patients in the dermatologic clinic. Eleven, or 23%, gave a mild dermographism. None of the reactions were "too prominent." In five patients with chronic urticaria, all showed some dermographism.

Sir Thomas Lewis[3] found amongst young, healthy individuals, conspicuous whealing of the skin as a sequel to firm stroking in about 5% of those tested. Mumford[4] states that the common varieties of urticaria show altered response to

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1. Urbach, E., and Gottlieb, P. M.: Allergy, Ed. 2, New York, Grune & Stratton, Inc., 1946, p. 181.

2. Walzer, A.: Urticaria: Experimental Urticaria Factitia, Arch. Dermat. & Syph. **18**:868-886 (Dec.) 1928.

3. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

4. Mumford, P. B.: Urticaria Factitia, Brit. J. Dermat. **38**:444-447 (Nov.) 1926.

mechanical stimulation; and very often in patients with chronic urticaria the drawing of a blunt point with a pressure of 2 lb. (1 kg.) will produce a wheal within a few seconds. Graham and Wolf [5] reported a series of 30 unselected cases of urticaria in which every one of the patients with urticaria manifested dermographism. It is interesting to note that Graham and Wolf state that the dermographism was not apparent until "stressful" interviews had altered the state of the patient's blood vessels. Sulzberger and Baer [6] in discussing Graham and Wolf's article point out that, in their experience, by no means all cases of true urticaria are associated with dermographism.

Likewise, we have not believed that dermographism is an inevitable or even a common accompaniment of subacute or chronic urticaria.

In order to test the correctness of our impressions, we studied 100 patients with subacute or chronic urticaria, 100 dermatologic patients without urticaria, and 20 patients with obvious and severe dermographism.

EXPERIMENTS

All the patients were tested by firm stroking with a tongue depressor. Patients were said to show dermographism when this stimulus produced a distinct and conspicuous linear wheal. While individuals differed greatly in the size of the wheal produced, the difference between those who showed dermographism and those who did not was clear-cut.

TABLE 1.—*Incidence of Dermographism in Nonurticarial Dermatoses*

No. of Cases	Nature of Dermatoses	No. Showing Dermographism
9	Atopic dermatitis	1
21	Allergic contact eczematous dermatitis	1
70	Miscellaneous dermatoses	3

One hundred consecutive patients without urticaria seen in the Allergy Section were tested for dermographism. Table 1 shows that in this group five patients responded with distinct dermographism.

The patients with atopic dermatitis were tested on uninvolved areas. Patients with atopic dermatitis frequently showed white dermographism in the involved areas, but only one patient with atopic dermatitis showed true dermographism. The incidence of 5% dermographism in this series of nonurticarial dermatoses corresponds exactly with the figures that Lewis [3] gives for distinct dermographism among "perfectly healthy individuals."

One hundred consecutive patients with subacute or chronic urticaria were also tested for dermographism. The urticaria had been present for at least three weeks, and many of the patients had had urticaria for many months. All these patients

5. Graham, D., and Wolf, S.: Pathogenesis of Urticaria: Experimental Study of Life Situations, Emotions, and Cutaneous Vascular Reactions, J. A. M. A. **143**:1396-1402 (Aug. 19) 1950.

6. Sulzberger, M. B., and Baer, R. L., in editorial comment on Graham and Wolf,[5] The 1950 Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1951, p. 164.

were tested when the urticaria was present. Table 2 shows that in this series of 100 consecutive cases the incidence of dermographism was 6%.

In this material, then, a possible allergic mechanism could be demonstrated in 19% of all cases of chronic urticaria. In only 6% of all cases was there any dermographism.

COMMENT

As Sulzberger and Baer [6] point out, confusing dermographism with common chronic urticaria is regrettable, since it compounds the difficulty of treating these already formidable entities. We have seen many patients with dermographism, in

TABLE 2.—*Incidence of Dermographism in Subacute and Chronic Urticaria*

No. of Cases	Cause of Urticaria	No. Showing Dermographism
12	Penicillin	1
2	Acetylsalicylic acid	0
2	Giardia lamblia	0
1	Lymphoblastoma	0
1	Milk	0
1	Tetanus antitoxin	0
81	Unknown	5

the past two years, who had received elimination diets and various scratch and intracutaneous tests under the mistaken impression that they were suffering from chronic urticaria. Naturally, they had a great many "positive" reactions which were meaningless. Incidentally, in a series of 20 patients with severe dermographism without urticaria, we could find no allergic mechanism involving such factors as drugs or foods in operation.

SUMMARY AND CONCLUSION

The incidence of dermographism in 100 patients with various dermatoses but without urticaria was 5%.

The incidence of dermographism in 100 patients with subacute or chronic urticaria was 6%, or about the same as in the control group.

In 19% of the cases of chronic urticaria, allergic factors could be found.

In dermographism no allergic factors were found.

There seems to be no necessary relationship between chronic urticaria and dermographism.

ISONIAZID THERAPY OF CHRONIC DERMATOSES

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AND
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THIS STUDY is a continuation of our interest in the treatment of tuberculodermas [1] and those skin diseases which in the past have been thought to be linked with tuberculosis. As is often the case we have too few cases, but we hope that this investigation will stimulate more reports and thus give a broader interpretation of the value of isoniazid treatment of this interesting group of skin diseases.

REPORT OF CASES

Erythema Induratum.—In three cases the Bazin type of erythema induratum was treated with isoniazid. We submit short summaries of the cases.

CASE 1.—W. N., a white man, aged 27, was seen by H. J. L. in February, 1952. The patient was treated with calciferol without benefit, and new lesions continually developed. A biopsy on June 23, 1952, confirmed this diagnosis. A tuberculin test was not done. The lesions were present as deep nodules on the lower legs, some of which gradually broke down and ulcerated. In July, 1952, the patient was given 200 mg. of isoniazid daily, and, because of the associated marked cellulitis, supportive treatment with penicillin. The latter treatment was discontinued as soon as the acute inflammatory reaction had subsided. In September, 1952, marked improvement was noted, and the dosage of the drug was reduced. As of January, 1953, no new lesions had appeared, and by this time all the former lesions had involuted. The patient, because of his occupation as a policeman, refused a post-treatment biopsy.

CASE 2.—W. M., a Negro woman, aged 28, was seen in the Dermatology Clinic at the Cincinnati General Hospital in February, 1952. On the calves of both legs she had numerous deep painful nodules, which had been present since 1947. A biopsy confirmed the clinical impression. The tuberculin test was positive. In March, 1952, the patient was started on treatment with isoniazid, 200 mg. daily. This was continued until September of the same year. During this

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The histopathological reports, unless otherwise stated, were interpreted by Dr. D. Richfield, histopathologist to the Department of Dermatology.

From the Department of Dermatology of the University of Cincinnati College of Medicine (Dr. Goldberg, Assistant Professor; Dr. Simon, Resident).

The microphotographs were done through the courtesy of Mr. J. B. Homan, Director of Medical Arts, University of Cincinnati College of Medicine.

The isoniazid used in this report was furnished by The Wm. S. Merrell Company. The 5% isoniazid cream (Dinacrin) used in this report was provided by Winthrop-Stearns, Inc.

The following dermatologists through their contribution of cases helped make this study possible: M. Feldman, D. Kindel, R. Kile, H. J. Lavender, W. McDaniel, R. Preston, and A. Weiner.

1. Goldberg, L. C., and Simon, C. R.: The Treatment of Lupus Vulgaris with Isoniazid: Report of 2 Cases, J. A. M. A. **151**:640-642 (Feb. 21) 1953.

time no new lesions appeared, and the treatment was stopped. New lesions reappeared six weeks later, and the therapy was again given until the present time. There have been no new lesions and the older ones have completely involuted. A post-treatment biopsy was done and revealed complete disappearance of the entire pathological process.

CASE 3.—R. T., a white woman, aged 37, was seen by R. P. in February, 1952. The patient had deep-seated nodules and old scars with hemosiderin deposits on the calves of both legs.

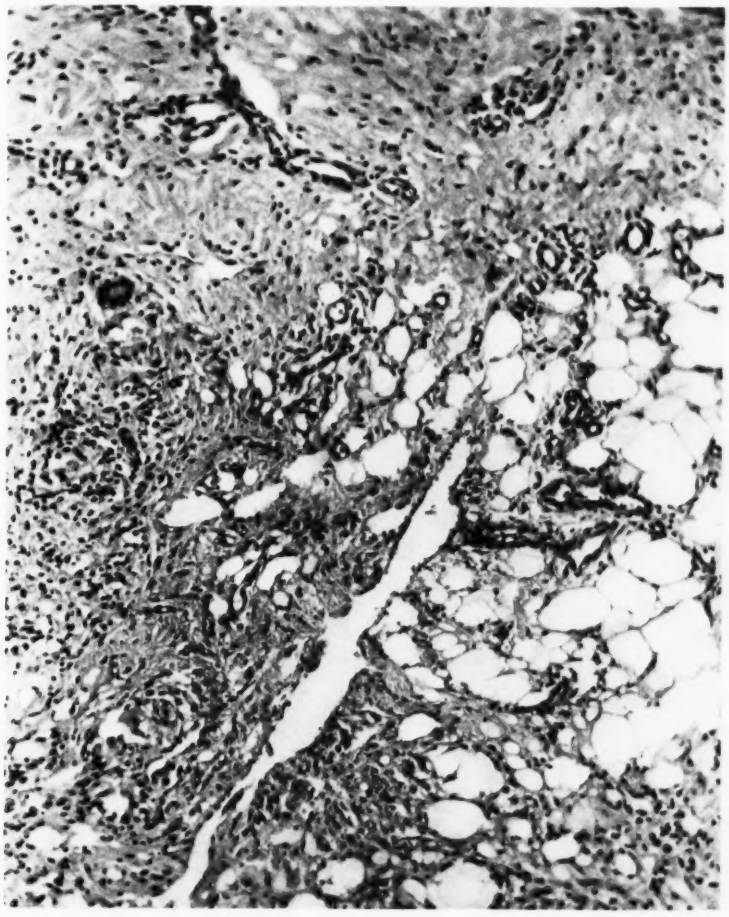

Fig. 1.—Erythema induratum (Bazin type) before isoniazid treatment.

These had been present for about two years. There had been no response to previous treatment with paraaminosalicylic acid. A biopsy confirmed the clinical impression, but a tuberculin test was not done. The patient was started on isoniazid treatment, 200 mg. daily, in March, 1952. This was increased to 300 mg. daily until December, 1952. All active lesions have disappeared. No post-treatment biopsy was available.

Lupus Miliaris Disseminatus Faciei.—Three patients with lupus miliaris disseminatus faciei were seen by three independent observers. Biopsies confirmed the

diagnoses in the three patients, all of whom were seen at the October meeting of the Cincinnati Dermatological Society. Two of the three patients were treated with isoniazid, 5 mg. per kilogram of body weight, with excellent results. At the time of this writing no post-treatment biopsies have been made, but the patients have been reported as doing well. The third patient, did not respond to isoniazid treatment

Fig. 2.—Erythema induratum (Bazin type) after isoniazid treatment.

even though he received 250 mg. daily. This patient was also given 5% isoniazed cream locally without any success. No tuberculin tests were done on any of these patients.

Papulonecrotic Tuberculid

W. M., a Negro woman, aged 34, was seen at the Cincinnati General Hospital Dermatology Clinic. Her past history revealed that her mother and father both died of tuberculosis. The patient stated that she had had multiple, excoriated, and ulcerated papules on her extremities

for 10 years. A biopsy confirmed the clinical impression of papulonecrotic tuberculid. The tuberculin test was positive. Isoniazid, 250 mg. daily, was started in June, 1952, and increased to 300 mg. daily. Until September new lesions appeared intermittently, but since that time there has been no activity. Isoniazid treatment was discontinued in October, 1952, and up to the present time there have been no new lesions. A post-treatment biopsy revealed no further active inflammatory reaction.

Fig. 3.—Papulonecrotic tuberculid before isoniazid treatment.

Tuberculosis Cutis Lichenoides (Lichenoid Papular Tuberculid)

C. R., a Negro woman, aged 32, was seen at the Cincinnati General Hospital Dermatology Clinic in August, 1952. At this time she had an eruption on her neck and upper extremity which had been present for several weeks. The skin lesions were small glistening pinkish white papules. These were confluent and pruritic. A biopsy of a group of these lesions confirmed the clinical impression of a lichenoid papular tuberculid. The tuberculin test was negative. Isoniazid treatment was started on Aug. 21, 1952, and the patient was given 400 mg. daily. This was continued until Nov. 5, 1952. The eruption was almost completely gone after one month's treatment. A post-treatment biopsy revealed an almost complete disappearance of the inflammatory process.

Tuberculous Ulcer

G. N., a Negro woman, aged 33, was seen at the Cincinnati General Hospital Dermatology Clinic in July, 1952. The patient presented a 9 by 7 mm. ulcer on the right side of her neck, which she stated had been present for one month. The edges were raised, and the base was granulomatous. There was no associated lymph adenopathy. An x-ray of the chest revealed two small cavities in the apex of the right lung as well as a dense infiltrate. A biopsy confirmed

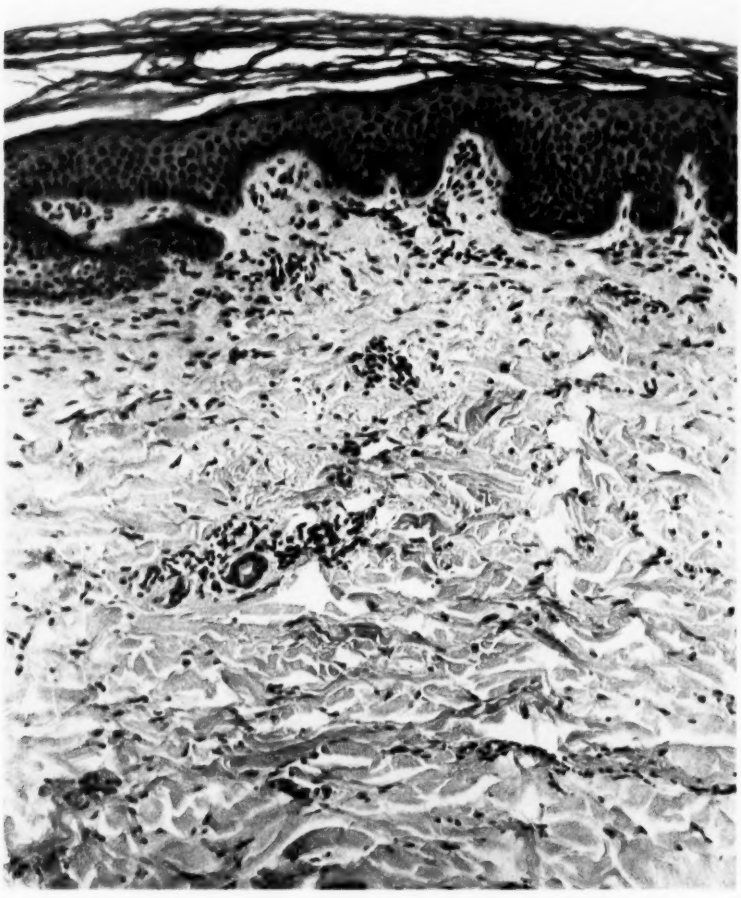

Fig. 4.—Papulonecrotic tuberculid after isoniazid treatment.

the diagnosis of a tuberculous ulcer. No tubercle bacilli were demonstrated in the histopathological section. The tuberculin test was positive, and a culture of tissue from the ulcer was positive for tuberculosis. Isoniazid treatment of 300 mg. daily was started on Aug. 11, 1952, and by Sept. 23, 1952, the ulcer was practically healed. A post-treatment biopsy was not done, since the patient was transferred to the Dunham Tuberculosis Sanatorium.

Sarcoidosis

H. F., a white woman, aged 35, was seen on Oct. 21, 1952, by R. K. because of a skin eruption on her left elbow. This had been present for four weeks. The lesions were arranged in a

linear pattern and were made up of skin-colored papules. Occasional isolated lesions were also seen on the right palm and knee. A biopsy of a lesion revealed the microscopic pattern of sarcoidosis, which was interpreted by Dr. Zola Cooper of St. Louis. An x-ray of the chest was reported as follows: "The findings in the lungs are compatible with the diagnosis of sarcoidosis." A new lesion developed on the patient's ankle on Nov. 17, 1952, at which time she was started on isoniazid treatment, 100 mg. daily. A month later this was increased to 150 mg. daily and finally to 200 mg. daily. The patient received seven weekly treatments of x-rays, 88 r., to the

Fig. 5.—Lichenoid papular tuberculid before isoniazid treatment.

lesions on her elbow and ankle. On Jan. 9, 1953, the patient was markedly improved, and no new lesions have appeared up to the present time. It is reported that the lesions on the other portions of the body which did receive x-ray therapy also disappeared. A post-treatment biopsy or an x-ray of the chest has not been done up to the present time.

Chronic Discoid Lupus Erythematosus.—Ten patients with chronic discoid lupus erythematosus were treated with isoniazid from three weeks to three months. The dosage was 5 mg. per kilogram of body weight. Six of these patients were also

treated locally with 5% isoniazid cream. This was applied two to three times daily to the active lesions. Not one single patient reported or was seen to have benefited by the use of isoniazid orally or locally.

Subacute Disseminated Lupus Erythematosus.—Nine patients with subacute disseminated lupus erythematosus, six of whom had positive L. E. cells, were treated

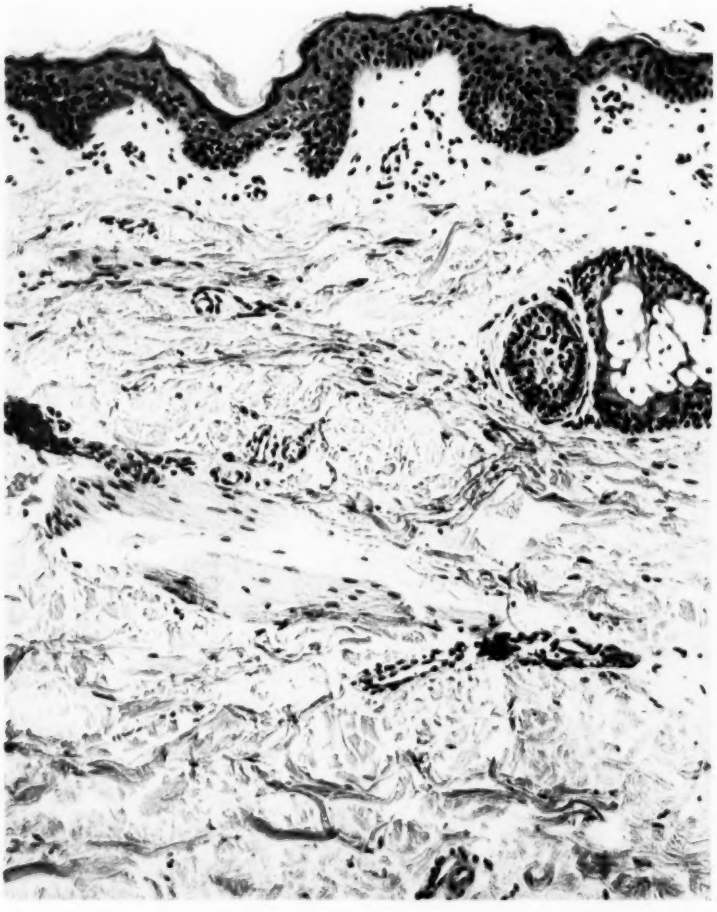

Fig. 6.—Lichenoid papular tuberculid after isoniazid treatment.

with isoniazid for an average of six weeks on a schedule of 5 mg. per kilogram of body weight. In a number of these patients not only was there no response to treatment, but in several of them new lesions developed while the drug was being given. Some of these patients had previously improved on cortisone therapy, and when isoniazid was substituted to see whether this drug would hold the disease in check all of the patients became worse. These were not interpreted as rebound failures. Three of these patients were given 5% isoniazid salve locally, but without any

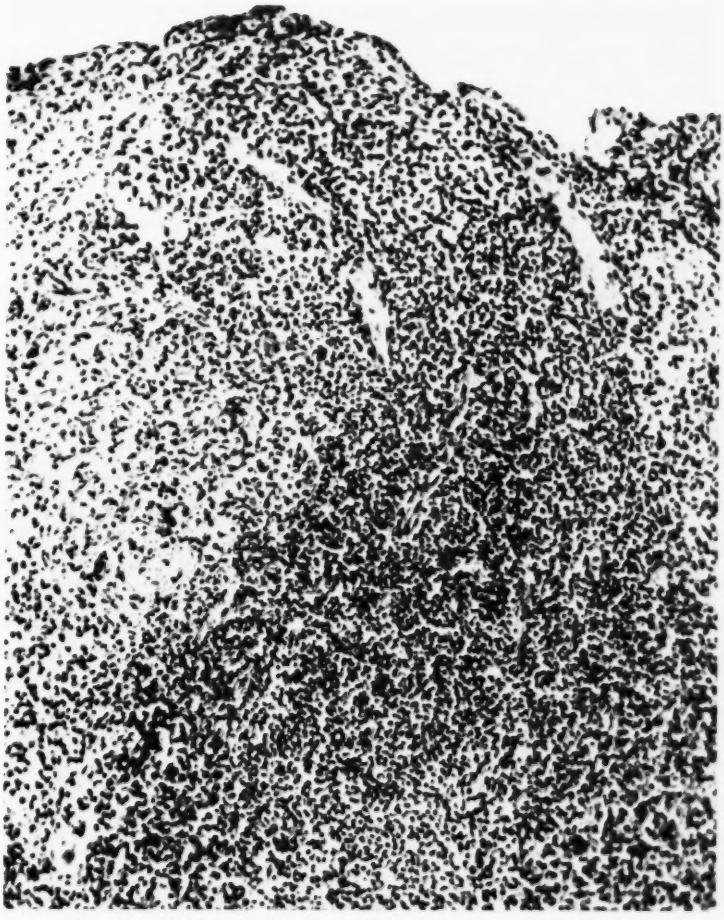

Fig. 7.—Tuberculous ulcer before isoniazid treatment.

Therapeutic Response to Isoniazid

Diagnosis	Duration of Treatment	Daily Dosage	Reactions	Response
Erythema induratum	6 mo.	200 mg.	None	Excellent
Erythema induratum	8 mo.	200 mg.	None	Relapse when treatment stopped; re-treatment result excellent.
Erythema induratum	6 mo.	200 mg.	None	Excellent
Lupus miliaris disseminatus faciei	4 mo.	250 mg.	None	None
Lupus miliaris disseminatus faciei	5 mo.	300 mg.	None	Improved
Lupus miliaris disseminatus faciei	6 mo.	400 mg.	None	Excellent
Papulonecrotic tuberculid (1 case)	10 wk.	300 mg.	None	Excellent
Lichenoid tuberculid (1 case)	9 wk.	400 mg.	None	Excellent
Tuberculous ulcer (1 case)	6 wk.	5 mg. kg.	None	Excellent
Sarcoidosis (1 case)	2 mo.	150-200 mg.	None	Improved
Chronic discoid lupus erythematosus (10 cases)	3 wk. to 3 mo.	5 mg. kg.	None	None
Subacute disseminated lupus erythematosus (9 cases)	6 wk. average	5 mg. kg.	None	None

improvement. One patient in this group reported improvement for 40 days while on isoniazid, and this was substantiated clinically three weeks after treatment had been started. Nevertheless, when the patient was seen two months later, not only was there no improvement, but new lesions were appearing on the face and neck. The drug was discontinued.

COMMENT

This is a small but representative group of cases insofar as the tuberculodermas are concerned. Unfortunately, some of these patients were seen privately and such data as results of biopsy before and after treatment and routine tuberculin tests are incomplete. Had we had a larger series of cases and more accurate tuberculin reactions, it would have been extremely interesting to note the responses to the tuberculin tests and the biopsy findings before and after treatment with isoniazid. We contemplate further study on this problem.

It was our impression that the rate and speed of healing of the various tuberculodermas corresponded to Michelson's [2] chart. He noted that erythema induratum and lupus miliaris disseminatus faciei tend to heal slowly. In our cases the average time necessary to obtain an excellent response was six and one-third months, although all three patients showed improvement within three to six weeks of treatment with isoniazid. All of these patients have remained lesion free since they were last examined. One patient had a relapse when the drug was stopped too early, but the disease subsided after treatment was resumed. The post-treatment biopsy in the one patient demonstrated excellent response to this drug. At this time, we should like to entertain a belief that it may be possible through treatment of erythema induratum with isoniazid to distinguish between the vascular and Bazin types. From our studies it is our impression, even though we have not as yet treated any of the vascular types of this disease, that they might not respond to isoniazid therapy. This theory remains to be proved. Lupus miliaris disseminatus faciei is also said to heal slowly, and in our series of three cases, in two of which the disease responded to isoniazid treatment and in one of which it was refractory, the average length of treatment was four and two-thirds months. Although we have no post-treatment biopsy reports in any of these cases, the clinical impression must be accepted until such biopsies are available. We are unable to explain the absence of clinical response in the refractory case, but Michelson states, "Not only does immunity change in patients with tuberculosis of the skin, but the degree of allergy changes." This might be the answer.

On the other hand, the response to treatment by the lichenoid tuberculid, the papulonecrotic tuberculid, and the tuberculous ulcer was a matter of weeks. The average time for a successful result was nine weeks. This also corresponds to Michelson's chart.

The sarcoidosis case is a bit confusing since x-ray therapy was added to the therapeutic regimen, but the report states that the response was accelerated after isoniazid treatment was instituted, and this was further borne out by the fact that lesions which were not treated by x-ray also responded to treatment. It would be still more conclusive if we had post-treatment biopsies and further reports on the x-rays of the chest, but unfortunately the patient lives out of town and is not always

2. Michelson, H. E., and Laymon, C. W.: Classification of Tuberculosis of the Skin, Arch. Dermat. & Syph. **52**:108-113 (Aug.) 1945.

easily contacted. The fact that in this case sarcoidosis responded to isoniazid treatment does not in any way mean that the disease has a tuberculosis etiology, but if in the future in similar cases there is a response to this form of therapy, it may help establish the missing link between sarcoidosis and tuberculosis. This particular subject gives much food for thought.

We are neither surprised nor disappointed that the cases of chronic discoid lupus erythematosus and subacute disseminated lupus erythematosus did not respond to isoniazid therapy. Our studies with the other patients led us to believe that we could not expect a favorable response. This negative reaction was further borne out by the fact that none of the patients responded to local therapy with the isoniazid ointment. All of the patients in this series were given a fair test with the drug not only as to dosage, but also in length of time that the drug was given.

It is interesting to note that during this study no patients reported nor did we note any untoward reactions to this drug.

Cordero [3] reported immediate response to isoniazid in the treatment of rosaceal tuberculid, scrofuloderma, and tuberculosis orificialis cutis. His results in lupus vulgaris were a favorable change after the third to fourth week, with healing after the fifth to eighth week. He reported negative results with lupus erythematosus and sarcoidosis. His dosage was 10 mg. per kilogram of body weight; this was definitely more than our schedule. He achieved excellent results in the responsive cases.

Although we have not had the opportunity to treat leprosy, we feel that we should make note of the fact that a report was made to the annual meeting of the American Society of Tropical Medicine and Hygiene, Nov. 19, 1952, in Galveston, Texas, by Drs. Latapi, Rodriguez, Rubio, and Estrado [4] on the successful treatment of this disease by isoniazid. They stated that 13 of 14 patients showed improvement; that nodules on the skin decreased in size and number and in some cases almost disappeared. New lesions did not develop while the patient was under treatment, and tissue samples following treatment showed a reduction in the number of Mycobacteria leprae (Hansen bacilli) in the infected tissue. The one patient that failed to respond had tuberculoid leprosy. Saiwaka stated that 5 of 14 patients treated with isoniazid recovered completely, and the disease was stopped in the other 9.

SUMMARY AND CONCLUSION

Not only has lupus vulgaris [5] responded to isoniazid therapy, but so have erythema induratum (Bazin type) in three cases, lupus miliaris disseminatus faciei in two cases, lichenoid tuberculid in one case, papulonecrotic tuberculid in one case, tuberculous ulcer in one case, and sarcoidosis in one case. Chronic discoid or subacute disseminated lupus erythematosus has in no case responded to isoniazid, whether given orally or locally.

623 Doctors Building, Cincinnati.

3. Schoch Letter, Dallas, Texas, Feb. 1953.

4. The Star, Carville, La., Feb. 1953.

5. Obermayer, M. E.; Wilson, J. W., and Smith, P. N.: Isonicotinylhydrazine (Rimifon ®) in the Treatment of Lupus Vulgaris: Report of a Case, J. Invest. Dermat. **19**:311-313 (Nov.) 1952.

LABORATORY TEST FOR EVALUATION OF FUNGICIDAL SOLUTIONS

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LABORATORY procedures for the in vitro testing of fungicidal agents were pioneered by Schamberg and Kolmer [1] in 1922. Their method consisted of exposing a homogeneous fungus-spore suspension, obtained by agitation with glass beads, to varying dilutions of the test substances. Tests developed subsequently by McCrea,[2] Emmons,[3] and Hillegas and Camp [4] also utilized microconidial or spore suspensions. However, in 1939, Burlingame and Reddish [5] expressed the opinion that spore suspension methods failed to parallel clinical conditions and did not take into consideration the characteristic of penetrability of the fungicidal agent. Their method consisted of exposing mycelial masses cultivated on Sabouraud agar to fungicidal solutions for varying periods of time, transferring cork-borer-cut sections of the mat, first to aqueous broth for washing and thence to Sabouraud agar for growth. Subsequently, Golden and Oster [6] showed that the aqueous-broth wash did not remove alcohol-soluble, water-insoluble fungicides from the mycelial mass. They suggested the use of 30% acetone in water as a wash to remove all traces of alcohol-soluble fungicides. These test modifications, in our opinion, have not adequately assayed penetrability, a characteristic of extreme importance in a fungicidal agent. Laboratory studies too frequently fail to give an accurate picture of the relative value of a fungicidal agent, owing, in part, to the failure to introduce the problem of penetrability in such tests.

This work was assisted by a grant from the Smith, Kline & French Laboratories for mycological research.

From the Department of Dermatology (Clarence S. Livingood, M.D., Director), University of Texas School of Medicine.

1. Schamberg, J. F., and Kolmer, J. A.: Studies in the Chemotherapy of Fungus Infections, Arch. Dermat. & Syph. **6**:746, 1922.

2. McCrea, A.: A Proposed Standard Method for Evaluation of Fungicides, J. Lab. & Clin. Med. **17**:72, 1931.

3. Emmons, C. W.: Fungicidal Action of Some Common Disinfectants on 2 Dermatophytes, Arch. Dermat. & Syph. **28**:15, 1933.

4. Hillegas, A. B., and Camp, E.: The Testing of Fungicides Insoluble in Water, J. Invest. Derm. **6**:217, 1945.

5. Burlingame, E. M., and Reddish, G. F.: Laboratory Methods for Testing Fungicides Used in the Treatment of Epidermophytosis, J. Lab. & Clin. Med. **24**:765, 1939.

6. Golden, M. J., and Oster, K. A.: Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds: II. Evaluation of a Fungicidal Laboratory Method, J. Am. Pharm. A. (Scient. Ed.) **36**:359, 1947.

A satisfactory method of growing compact, discrete fungus colonies was not available before 1947. In that year, Littman [7] introduced a new culture medium for the isolation and identification of fungi. In addition to its use in isolation of pathogenic fungi from bacterially contaminated material, this new medium has been found to be ideal for the in vitro testing of fungicidal solutions. The present study was undertaken in an attempt to develop a simple fungicidal culture technique which would require more penetrability of a fungicide than other available tests. This was made possible by utilizing the compact type of colonial growth on Littman oxgall agar (Difco).

METHODS AND MATERIALS

The test fungus was cultivated on Sabouraud dextrose agar for three weeks, at which time the mature culture was emulsified in 2 ml. of sterile distilled water. A 1:5 dilution of the suspension was plated on Littman oxgall agar (Difco) with a platinum loop, in the same manner as that employed in streaking bacterial cultures. Plates were incubated for eight days at 27 C. Figure 1 shows an eight-day growth of Trichophyton purpureum plated in such a manner. The simultaneous streaking of many plates of medium with the culture makes numerous colonies of the same age and approximate size available for the test.

The technique of fungicidal assay follows: 1. The test fungicidal solution was poured over a plate containing eight-day-old colonies and allowed to remain in contact for 60 seconds. The test solution was then poured off. 2. The plate and its colonies were then washed for three minutes with cold running tap water. 3. The plate was then flooded with 25 ml. of 30% acetone in water, which was allowed to remain in contact with the colonies for five minutes. 4. The plate was again washed with running water for three minutes. 5. By means of a sterile needle, an intact colony was then transplanted to a slant of Sabouraud dextrose agar, in which was incorporated 200 γ per milliliter of neomycin. Slants were maintained at room temperature, and record was made of the presence or absence of growth at the end of two weeks.

Selection of Culture for Fungicidal Assay.—T.purpureum was selected as the test organism because of its uniform growth of firm, compact colonies on Littman oxgall agar. After eight days of incubation at 27 C., each colony was approximately 3 mm. in size, small enough to facilitate planting in small culture bottles. Eight-day-old cultures were preferred to others because of the appearance, by that time, of mature microscopic characteristics. However, cultures 6 to 14 days old were tested by this method and found to give no variation in the end-result.

Application of the Fungicide.—The Burlingame-Reddish method of application of the fungicide, by pouring the solution on an intact plate, was adopted. This procedure requires that the test fungicide penetrate fungal elements on an intact plate; and technically it proved to be a simple procedure. A standard contact time of 60 seconds was adopted for screening purposes. Increments of time up to six minutes and down to a minimum of 30 seconds permitted further classification of fungicides in relation to each other.

Removal of the Fungicide from the Culture.—Although the water-soluble fungicides were removed by washing in running water, alcohol-soluble compounds were retained in part. Since 30% acetone in water did not inhibit the growth of T. purpureum up to a 30-minute exposure time, we have adopted its use as a wash, as recommended by Golden and Oster. Acetone is an effective solvent, especially for the fatty acids. According to Deuel,[8] caprylic and pelagonic acid show infinite solubility at 20 C., while the higher fatty acids are likewise soluble, although to a slighter degree. Johnson [9] substituted 50% isopropyl alcohol in water for the washing and found

7. Littman, M. L.: A Culture Medium for the Primary Isolation of Fungi, Science **106**:109, 1947.

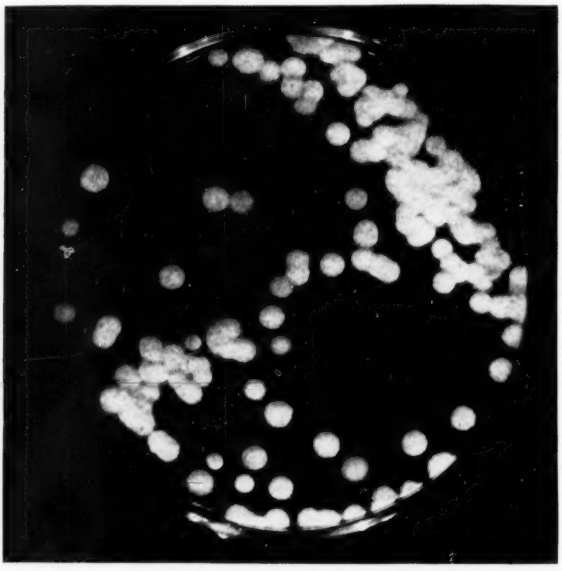
8. Deuel, H. J., Jr.: The Lipids: Their Chemistry and Biochemistry, New York, Interscience Publishers, Inc., 1951, Vol. 1.

9. Johnson, E. A.: Personal communication to the authors.

no variation in the end-result. However, he did note that 70% isopropyl alcohol itself was fungicidal when allowed to remain in contact with colonies of T. purpureum on Littman oxgall agar for 30 to 40 minutes.

Avoidance of Contamination.—The use of Littman oxgall agar eliminates the problem of saprophytic mold contamination and allows technical freedom in performing the test. Mold contamination, if it occurs, is of no consequence, because on oxgall agar all fungi grow discretely and separately without merging. Bacterial contamination is reduced by the presence of crystal violet and streptomycin. On the final planting from Littman oxgall agar to Sabouraud dextrose agar, bacterial contamination is prevented by the addition of 200 γ per milliliter of neomycin in the latter medium.

Fungicides Tested.—A number of commercial and prescription compounds were tested by this method. The commercial preparations were used without change, but the prescription preparations were dissolved in 70% isopropyl alcohol. It was realized that the base or solvent itself could



Eight-day growth of T. purpureum on Littman's oxgall agar.

influence the in vitro fungicidal activity, as well as the clinical results. However, an ideal laboratory test for the fungicidal activity of any compound should correlate as closely as possible with clinical results. As a result of clinical experience with most of the commercial compounds tested, it is our opinion that partial correlation may be possible. The following formulas were tested:

Formula A

Sodium propionate	2%
Sodium caprylate	2%
Undecylenic acid	5%
Propionic acid	3%
Salicylic acid	5%
Copper undecylenate	0.5%
Aerosol OT	0.1%
Water, distilled	20%
Isopropyl alcohol (91%) q. s.	

Formula B: Quatrasal (Dome Chemical, Inc.), consisting of:

Salicylanilide (Shirlan Extra)	5%
Hyamine 3258*	1%
Isopropyl alcohol	94%

Formula C: Desenex (Wallace & Tiernan Products, Inc.)

Undecylenic acid	10%
Isopropyl alcohol with propylene glycol and distilled water (pH 6.5)	40%

Formula D:

Asterol dihydrochloride	5%
Isopropyl alcohol (70%) q. s.	

Formula E: Sopronol (Wyeth, Inc.)

Sodium propionate	12.3%
Sodium caprylate	10.0%
Propionic acid	2.7%
Aerosol OT	0.1%
Inert ingredients	74.9%
Propyl alcohol	12.5%

Formula F: Decupryl (Crookes Laboratories, Inc.)

Copper undecylenate	10.0%
Undecylenic acid	5.0%
Aerosol OT, tetrachloroethylene and isopropyl alcohol	

Formula G: Octofen (McKesson & Robbins, Inc.)

8 hydroxyquinoline benzoate in 48% ethyl alcohol by volume

Formula H

Salicylic acid	6%
Benzoic acid	12%
Aerosol OT	0.1%
Isopropyl alcohol (70%) q. s.	

Formula I

Sodium propionate	2%
Sodium caprylate	2%
Undecylenic acid	5%
Isopropyl alcohol (70%) q. s.	

Formula J

Resin of podophyllin	0.2%
Isopropyl alcohol (70%) q. s.	

Formula K

Salicylic acid	20%
Aerosol OT	0.1%
Isopropyl alcohol (70%) q. s.	

Formula L

Caprylic acid	20%
Aerosol OT	0.1%
Isopropyl alcohol (70%) q. s.	
Isopropyl alcohol with propylene glycol and distilled water (pH 6.5)	40%

* Trimethylcetyl ammonium pentachlorophenate.

Formula A was devised by one of us (R. E. L.) and Capt. Jack W. McNamara, Medical Service Corps, United States Army, Chief of Pharmacy, Walter Reed Army Hospital, Washington, D. C. This hydroalcoholic mixture of several fatty acids, their sodium and copper salts, salicylic acid, and dioctyl sodium sulfosuccinate (Aerosol OT) in isopropyl alcohol was originally formulated for the treatment of resistant infections due to T. purpureum. It has been used in brief clinical trials at the John Sealy Hospital, Galveston, Texas, and the Walter Reed Army Hospital, Washington, D. C., with favorable results in most cases. Preliminary clinical trials with this mixture indicate that it is as effective as, if not more so than, the fatty acid formulas commercially available—Desenex (zincundecate), Sopronol (propionate-caprylate mixtures), Timofax (preparation containing 10% undecylenic and potassium salt), etc., Asterol (2-dimethylamino-6-[β-diethylaminoethoxy] benzothiazole), and benzoic and salicylic acid ointment (Whitfield's ointment). Only one compound tested, Quatrasal, approached the in vitro effectiveness of Formula A against T.purpureum. Since we have had no clinical experience with Quatrasal, we are unable to compare its in vitro activity with clinical effectiveness.

TABLE 1.—*Level of Fungicidal Activity: Golden-Oster Versus Proposed Method After One Minute Contact Time**

Method	Salicylic Acid			Caprylic Acid			Undecylenic Acid		
	5%	10%	20%	5%	10%	20%	5%	10%	20%
Golden-Oster	G	0	0	..	0	0	0	0	0
Proposed	G	G	G	G	G	G	G	G	0

* G indicates growth; 0, no growth.

TABLE 2.—*In Vitro Fungicidal Activity of Compounds Tested by Proposed Method*

Solution	Time Required to Inhibit Growth, Min.
Formula A	1
Quatrasal (B)	1
Decupryl (F)	2
Desenex (C)	3
Formula H	3
Formula K	4
Octofen (G)	4
Formula I	4
Formula L	5
Sopronol (E)	6
Asterol (D)	6
Formula J	6+

RESULTS

In order to compare the severity of our method with that of Golden and Oster, we examined three fungicides in varying dilutions in 70% isopropyl alcohol with 0.1% Aerosol OT by both techniques. The result of this comparison is shown in Table 1.

With the Golden-Oster technique it would appear that 10% salicylic acid, 10% caprylic acid, and 5% undecylenic acid killed the fungas T.purpureum after one-minute contact time. These findings correspond, in part, with those originally reported by these investigators, who placed the fungicidal level of salicylic acid at 8% and of undecylenic acid at 2.5%. These authors did not report on the fungicidal level of caprylic acid. However, a level of fungicidal activity for salicylic and

caprylic acid of greater than 20% and for undecylenic acid of between 10% and 15% was found by our method. Although other reasons for this difference in results may develop through further investigation, the most obvious one is the difference in compactness of fungal elements grown on Littman oxgall agar and on Sabouraud agar.

Each compound tested was allowed to remain in contact with colonies of T.purpureum grown on Littman agar until the fungicidal level was reached. Although the test was originally devised as a screening method for fungicides in hydroalcoholic solutions, an attempt was made to place the commercial and prescription fungicides in order of their in vitro activity as measured by this method. Colonies of the test organism (T.purpureum) were exposed to increasing increments of time of one-minute duration until no growth resulted in five of six transplants. The results of this experiment are shown in Table 2.

All compounds tested were used repeatedly on at least five different strains of T.purpureum, with no significant variation in the results. Formulas A and B were applied to cultures of T.purpureum for a period of 30 seconds. Formula A was still fungicidal after 30 seconds, but Formula B was not.

SUMMARY AND CONCLUSIONS

The testing of fungicidal activity of solutions has been unsatisfactory because of the lack of a method requiring penetrability of the tested agent. Methods using spore or microconidial suspensions fail to take into account this requirement. Contact of the fungicidal test solution with mold growth on Sabouraud agar permits easy penetration of the relatively loose mycelium. For this reason, the fungicidal activity of many compounds is relatively high when tested in this manner. It is quite likely, therefore, that the absence of correlation between in vitro and clinical tests has been engendered by inadequate in vitro tests. Although laboratory studies cannot exactly duplicate clinical conditions in which fungi are found imbedded in keratin, it is possible that the more resistance to penetration by chemical agents offered by the fungus colony in the in vitro test, the more closely will it parallel clinical conditions. The method proposed herein requires strong initial fungicidal activity. The proposed method decreases some of the technical difficulties encountered with other tests. It eliminates the use of sterile cork-borers and multiple transferring of mycelium from tube to tube in washing. It reduces the chances of contamination. Time variations encountered with other methods are eliminated. It imposes a rigid test of the in vitro fungicidal activity of commercial fungicidal comopunds and their solvents. Although in vitro fungicidal tests are not exactly comparable to the killing of fungi imbedded in keratin, we believe the proposed test more closely simulates actual conditions than do other techniques.

Formula A was found to be more actively fungicidal than other compounds tested. In this instance, the in vitro activity of Formula A paralleled its clinical effectiveness in the treatment of active fungus infections due to T.purpureum.

Clinical Notes, New Instruments and Techniques

FUNGICIDAL ACTIVITY OF DIPHENYLPYRALINE

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The antihistaminic compound Diphenylpyraline (1-methyl-piperidyll-4 benzhydryl ether) has been reported to have marked in vitro antifungal activity against many of the common strains causing inflammatory changes in the human skin. Carson and Campbell [1] reported that this drug showed marked activity in vitro against Trichophyton rubrum, Microsporum gypseum, Microsporum lanosum, Epidermophyton floccosum, and Candida albicans. Sokoloff [2] reported clinical evaluation of this drug on 103 patients in New Jersey. Further clinical studies in the hot and humid climate of the Carolina coastal country were thought worth while. One hundred thirty-seven patients with various fungous infections of the skin as well as with a few miscellaneous dermatoses were treated.

One side-effect of the drug, a distinct antipruritic effect, was apparent in most of the cases and warranted trial in some miscellaneous dermatoses which are also reported here. Sensitization to the drug was noticeably absent, although some patients complained of burning of the skin the first 10 days of use when the concentration of the drug was raised to 4%. This disappeared on continuance of the medication of the same strength and immediately stopped when the concentration was lowered to 2%.

METHOD

A 2% ointment (2% Diphenylpyraline in a vanishing cream base which did not contain any polyethylene glycol, Carbowax) was used exclusively throughout the studies, except for the control studies, when the base alone was used. Paired comparison studies using the ointment on one side and the base only on the other side of the body were done in some cases. In others paired comparison studies with other fungicidal agents were done, and this method is being carried out with a larger series of patients for later reporting. Wet dressings of the material were not utilized.

Each patient was given a careful examination; scrapings of the lesions were examined microscopically after maceration with potassium hydroxide, and other scrapings and curettings were cultured on Sabouraud's medium by the perfume-flask method of Dr. J. Walter Wilson.[3] Culture mounts were studied at intervals. Fluorescent light was used on the skin and on the cultures. Frequent examinations of scales and scrapings under the microscope were performed. Six-month follow-up studies were done whenever possible.

The patients were instructed to freely rub the ointment into the lesions morning and night and were seen in the office and clinic at frequent intervals to note progress. The clinical results are shown in the accompanying table.

COMMENT

No cases of sensitization to the base alone or to the base with 2% Diphenylpyraline were noted. Some burning was evidenced when a 4%-strength ointment was tried temporarily in a few cases. This did not result in dermatitis, and the treatment was continued, with the

1. Carson, L. E., and Campbell, C. C.: The Inhibitory Effect of 3 Antihistaminic Compounds on the Growth of Fungi Pathogenic for Man, Science **111**:689-691 (June 23) 1950.

2. Sokoloff, O.: Clinical Evaluation of "Diphenylpyraline" as an Antifungal Agent, A. M. A. Arch. Dermat. & Syph. **64**:754-756 (Dec.) 1951.

3. Wilson, J. W., and Plunkett, O. A.: Practical Medical Mycology: The Culture of Fungi as an Office Procedure, Arch. Dermat. & Syph. **59**:414-429 (April) 1949.

effect disappearing after several days' application. The antipruritic effect was mentioned as a distinct help by the majority of the patients, and this effect was utilized in the small group of diseases other than mycotic in which the ointment was tried.

Fungous infections of the glabrous skin of the body, including the trunk, legs, arms, and crural areas, showed an excellent response to the treatment. Among the six failures were three cases of chronic recurrent resistant mycotic infection acquired when the patient was in military service in which there had been treatment by all possible other methods, including x-ray therapy, cryotherapy, use of benzothiazole, benzoic and salicylic acid ointment (Whitfield's ointment) with thymol and sulfur added, and carbol-fuchsin paint (Castellani's paint). Two of these proved to be T. rubrum (purpureum) on culture, with the other showing a M. gypseum infection.

A group of 12 patients were treated with only the ointment base for 21 days, with uniform failure to respond in any way. Another 12 patients, listed among the other mycotic groups, were given the placebo ointment during the course of therapy without being informed of the change and were allowed to use it for about a week before being given the active medication again. Half this group noticed lack of antipruritic effect or a deterioration of the condition.

Results of Use of Diphenylpyraline

Disease	Cases, No.	Duration of Therapy, Days	Results		
			Cure	Improvement	Failure
Fungous Infections					
Glabrous skin (body, crural, etc.)	40	7-40	25	9	6
Glabrous skin (placebo therapy)	12	21	..	1	11
Toewebs and plantar	25	18-25	18	4	3
Feet and trichophytid of hands	9	22	7	1	1
Hands only	10	25	4	5	1
Tinea versicolor	18	15	15	0	0
Anal mycosis	5	14	1	4	..
Paronychiae	3	25	3	..	0
Nonmycotic					
Paronychiae (monilial)	7	25	0	2	5
Psoriasis	5	30-40	0	3	2
Lichen simplex chronicus	6	21-30	1	4	1

Fungous infections of the toewebs and the plantar surfaces responded well to treatment. In two of the failures clinical and cultural characteristics of a resistant strain of T. rubrum (purpureum) were shown.

Fungous infections of the feet with trichophytid of the hands responded in the same way, but in a much shorter length of time.

Direct fungous infections of the palms, showing fungi on direct scrapings or on culture, also cleared well. Tinea versicolor cleared rapidly without exception. Mycotic infection of the perianal area was found in only five out of a much larger number of cases of pruritus ani, but in most instances neurogenic influences were also present, and much of the help was derived simply from the antipruritic effect of the antihistamine rather than from any fungicidal action. Mycotic paronychiae responded slowly but favorably. Monilial paronychiae not only did not respond but became worse under treatment.

The series of cases of psoriasis included several of the resistant pustular type. Tests for fungi were made before treatment, but no fungi were found. The antipruritic effect was perhaps the most noticeable one, but there was definite thinning of the discoid lesions and diminution in scaling.

Lichen simplex chronicus, especially of the suboccipital or nuchal type, was helped a great deal by the use of the ointment. In all these cases there was failure to show fungi on culture or by direct examination. Soothing antipruritic effects were most noticeable and were probably responsible for the improvement shown.

Further studies are in progress, with the comparison method of pairing therapeutic agents being used in the treatment of each patient. This has been done in some patients using a proprietary sulfur, salicylic acid and washed coal tar in greaseless base, benzoic and salicylic

acid ointment, and a benzothiazole cream, as well as with polyethylene glycol base alone, and the results so far in comparing Diphenylpyraline with the fungicidal agents named have shown almost equal clinical responses in healing time and disappearance of the lesions. A sufficiently large series of cases has not yet been completed for valid statistical comparison.

SUMMARY

An ointment containing 2% Diphenylpyraline (1-methyl-piperidyl-4 benzhydryl ether) was given a clinical trial in 137 cases of dermatitis, 126 of these being fungous or monilial infections.

While the percentage of failure is greater than that previously reported, in the majority of these cases treatment was given during a long and unusually hot summer in the Carolina coastal country, where the humidity was also high. Acutely moist and secondarily infected cases were not included. In 74 cases cure was obtained in a reasonable time (average, 21 days), in 33 cases there was much improvement, and in only 30 cases was there failure to show satisfactory clinical response. A number of the failures were patients carrying T. rubrum (purpureum) infections. More extensive study and clinical trial are indicated.

77 Rutledge Ave. (37)

RECURRENT, FIXED ERYSIPELAS-LIKE DERMATOPHYTID

Ineffectiveness of Antibiotics Reported in a Case

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Recurrent erysipelas-like manifestations of the legs and their relationship to fungus infections have been thoroughly discussed and investigated.[1] McGlasson's[1a] article focused attention on the phenomenon and its bacterial etiology.

Sulzberger and associates,[1b] Traub and Tolmach,[1c] Waisman,[1f] and Reiss[1g] advanced the concept that some of the cases represent dermatophytids.

The purpose of this paper is to focus attention on the ineffectiveness of antibiotics and to reemphasize the importance of fungicidal measures when the cause is mycotic. Reference to the use of antibiotics in active or prophylactic therapy of this condition has not been found.

REPORT OF CASE

Present Illness.—W. S., a 24-year-old white man, was admitted to Osaka Army Hospital on Feb. 1, 1952, with a diagnosis of recurrent cellulitis of the right leg. Approximately two hours before admission, the patient, who was well and at work, suddenly experienced a sharp chill followed by fever. The oral temperature was 103 F. Upon arrival at the hospital he complained of malaise, myalgia, and arthralgia. Oral temperature was 101 F.

From the Dermatological Section of the Medical Service, Osaka Army Hospital, Osaka, Japan. This case was referred by Colonel George M. Powell, Medical Corps, Chief of the Medical Service.

1. (*a*) McGlasson, I. L.: Recurrent Erysipelas of the Legs with Dermatitis of the Feet, Arch. Dermat. & Syph. **14**:679-682 (Dec.) 1926. (*b*) Sulzberger, M. B.; Rostenberg, A., Jr., and Goetze, D.: Recurrent Erysipelas-Like Manifestations of the Legs: Their Relationship to Fungous Infections of the Feet, J. A. M. A. **108**:2189-2193 (June 26) 1937. (*c*) Traub, E. F., and Tolmach, J. A.: An Erysipelas-Like Eruption Complicating Dermatophytosis, ibid. **108**:2187-2189 (June 26) 1937. (*d*) Yang, K. L.: Causal Relationship Between Epidermophytosis of Feet and Recurrent Erysipelas and Elephantiasis of Legs, Chinese M. J. **57**:161-167 (Feb.) 1940. (*e*) Goeckerman, W. H., and Wilhelm, L. F. X.: Recurrent Lymphangitis: Report of a Case with Unusual Features, California & West. Med. **55**:251-252 (Nov.) 1941. (*f*) Waisman, M.: Recurrent, Fixed Erysipelas-Like Dermatophytid, Arch. Dermat. & Syph. **53**:10-18 (Jan.) 1946. (*g*) Reiss, F.: The Relationship Between Chr. Epidermophytosis of the Feet and Recurrent Erysipelas-Like Manifestations, J. Clin. Med. **3**:13-16 (Jan.-March) 1938.

Past History.—Approximately nine months prior to admission the patient had been in an automobile accident. The right lower extremity was injured, and a black and blue discoloration with abscess formation at the junction of the upper and middle thirds of the anterior aspect of the leg resulted. Treatment consisted of the use of soaks and ichthammol ointment, incision, and drainage. A small scar at the site of incision was the only residual.

One month later the exact area which had been injured in the accident suddenly became acutely inflamed. Acetylsalicylic acid and penicillin were administered and warm saline compresses applied, and after six days only slight hyperpigmentation remained. X-rays of the underlying bone were normal.

A total of eight recurrences of constant size, shape, and area distribution ensued at three and four week intervals. With each episode the local and constitutional components became severer. Each attack lasted exactly six days despite the administration of adequate doses of penicillin, chlortetracycline (aureomycin), oxytetracycline (Terramycin), chloramphenicol (Chloromycetin), and streptomycin on successive occasions. The only other therapy was the use of saline or boric acid compresses and acetylsalicylic acid.

During his ninth attack the patient was seen in the dermatological clinic. Cool water compresses only were prescribed, and the process subsided in six days. He was advised to return for observation and therapy should another attack occur. He was given oxytetracycline and advised to take 1 gm. daily, starting seven days before the expected onset of the next attack. His estimation of the onset was in error by four days. Despite 11 days of oxytetracycline intake the 10th recurrence appeared.

Additional History.—The patient has had scaling of the feet as long as he could remember. At the age of 12 he experienced redness and swelling of both feet. This was diagnosed as "dye poisoning," and thereafter he had always worn white socks. No history of drug intake could be elicited.

Physical Examination.—The patient, having his 10th recurrence, did not appear in acute distress but did complain of malaise, fever, myalgia, and arthralgia. His temperature orally was 101 F. The only abnormal findings were those involving the lower extremities. There was a bluish-red discoloration over the junction of the upper and middle thirds of the anterior surface of the right leg. This was roughly elliptical, not sharply demarcated, and tender on pressure and measured 10 cm. by 5 cm. The overlying skin was taut, and all the muscles of that leg were tender on pressure. Considerable scaling of the soles and interdigital areas of both feet was present. Several small fissures and erosions could be seen between the toes and at the plantar-phalangeal crease.

Laboratory Data.—Laboratory examinations, including red blood cell counts, total and differential white blood cell counts, routine urinalysis, determination of the sedimentation rate, hematocrit reading, and a serologic test for syphilis, gave results within normal limits. No pathogenic bacteria were recovered from the open lesions on the feet. Roentgenograms of the chest and right lower extremity were normal.

Hospital Course.—Within 24 hours the patient was afebrile, and over a six-day period the leg inflammation subsided with the aid of bed rest and cool saline compresses. The dermatophytosis, proved by laboratory methods to be caused by Trichophyton purpureum, was controlled with 5% salicylic acid in 70% alcohol, undecylenic acid foot powder, and a fungicidal ointment.

Subsequent Course.—There have been no recurrences in 14 months. Routine foot hygiene is being followed, and undecylenic acid foot powder is being used.

COMMENT

The reported case meets most of the criteria enumerated by Sulzberger in his discussion of Waisman's [1f] presentation of recurrent, fixed erysipelas-like dermatophytids. The unavailability of trichophytin prevented investigative procedures with that antigen.

The ineffectiveness of prophylactic and active antibiotic therapy has not been reported previously, to the best of my knowledge. Sulfonamides have been reported as being ineffective in controlling the condition.[1d, e, g] In this case penicillin, streptomycin, oxytetracycline, and chloramphenicol were ineffective as therapeutic agents. Oxytetracycline given prophylactically for 11

days failed to prevent an attack. Therefore, it appears that antibiotic-sensitive organisms were not implicated in this process, and from the effectiveness of antifungal measures one might consider the condition a dermatophytid.

Pathogenic streptococci and staphylococci were not cultured, but one cannot be sure these organisms were not overlooked in our investigative procedures. Other antibiotic-resistant organisms (bacteria or fungi) could have been present and served as a nidus for the entire process. In addition, a combination of fungal and bacterial antigens may be necessary to sensitize the patient and elicit the erysipelas-like response. Another possibility is that the eliciting antigens are whole or parts of dead bacteria. Antibiotics would not prevent their presence and conceivably could provoke an attack by killing the bacteria. An antigen common to the living fungus on the feet and the antibiotic being used might complicate the picture. Systemic administration of antibiotics may not produce a local concentration of the drug sufficient to destroy the bacteria. Morphologic and physiologic changes, such as cicatrices and disturbances of the vascular and lymph supply, could lower the antibiotic supply locally.

Despite the possibility of investigative errors, antibiotic-resistant bacteria, and multiple etiologic agents, this case supports the concept of a recurrent, fixed erysipelas-like dermatophytid. It also emphasizes the fact that prophylactic treatment of fungus infections of the feet is of utmost importance. Whether or not the mycotic infection is the sole etiologic agent or supplies the mode of entry for itself or other organisms, successful treatment of the underlying disease should prevent recurrences.

SUMMARY

A case of a recurrent, fixed erysipelas-like dermatophytid is reported.

Ineffectiveness of active and prophylactic antibiotic therapy is discussed.

Treatment of the underlying fungus infection is emphasized.

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HEALING OF CHRONIC SICKLEMIA LEG ULCERS WITH CORTISONE THERAPY

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Sickle-cell anemia, a hereditary hemolytic anemia limited almost entirely to the Negro race, is a disease that may be so subtle as not to enter the mind of the clinician.[1] Winsor and Burch aptly termed it "a great masquerader."[2] It is characterized by the peculiar shape of the erythrocytes deprived of oxygen[1b] and is now thought to be due to abnormal hemoglobin, differing from that found in normal erythrocytes.[3] Sicklemia, the sickle-cell trait without symptoms, is said to occur in about 7% of the American Negro population,[4] whereas sickle-cell anemia occurs in 1 out of 40 patients with sicklemia.[5]

1. (*a*) Diggs, L. W.; Ahmann, C. F., and Bibb, J.: The Incidence and Significance of the Sickle Cell Trait, Ann. Int. Med. **7**:769-778 (Dec.) 1933. (*b*) Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia: Report of a Case Greatly Improved by Splenectomy, Arch. Int. Med. **39**:233-254 (Feb.) 1927. (*c*) Huck, J. G.: Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **34**:335-344 (Oct.) 1923.

2. Winsor, T., and Burch, G. E.: Sickle Cell Anemia, a "Great Masquerader" Easily Recognizable with Routine Use of Diagnostic Parameter, J. A. M. A. **129**:793-796 (Nov. 17) 1945.

3. Gray, G. W.: Sickle-Cell Anemia, Scient. Am. **185**:56-59 (Aug.) 1951.

4. Cooley, T. B., and Lee, P.: The Sickle Cell Phenomenon, Am. J. Dis. Child. **32**:334-340 (Sept.) 1926. Diggs.[1a] Gray.[3]

5. Diggs.[1a] Gray.[3]

Ever since the first case of sickle-cell anemia was described by Herrick in 1910,[6] chronic leg ulcers have been considered a common complication in adolescent and adult Negroes.[7] It is a more rare complication in young Negro children.

It is the purpose of this article to describe the healing obtained with two weeks of cortisone therapy of chronic leg ulcers in a Negro boy 9 years of age exhibiting the sickle-cell trait.

REPORT OF A CASE

G. T., a Negro boy, aged 9 years, was brought into the clinic from one of the summer camps for underprivileged children with a chief complaint of chronic leg ulcers of four months' duration. The child had been at the camp for one week and was treated by the camp nurse for this length of time without any regression of the leg ulcers. The ulcers had appeared after the patient had fallen out of bed four months prior to the examination. He had been seen in the dispensary at one of the neighboring large city hospitals one month after the occurrence of the ulcers and was given some "green salve" to apply to the lesions. There was no change in the condition of the ulcers, and the patient never returned to the hospital dispensary.

The patient had been a full-term spontaneous-delivery baby, developing in the normal manner as to sitting up, walking, and talking. He had had the usual childhood diseases. A tonsillectomy and adenoidectomy operation were performed at the age of 7, and he had several teeth extractions after that. The past history was otherwise noncontributory, except that the mother had always considered him a sickly child as compared with the other three children. The mother had been married twice, and the patient was the only child born to the first husband. The patient was always able to play with the other children and had never complained of undue fatigue. He was in the fourth grade of elementary school.

Physical examination revealed a well-developed but undernourished Negro boy, height 53 in. (135 cm.), weight 57 lb. (25.9 kg.), with bilateral leg ulcers. The blood pressure was 94/70 mm., pulse rate 80, and temperature 98.6 F. (37.0 C.). The sclerae were nonicteric. The pupils reacted normally to light and accommodation. Ophthalmoscopic examination revealed normal findings. Otic canals were clean, with the drums intact. The buccal mucosa was pale but nonicteric. The nailbeds were pale. There were no palpable cervical masses, nor was there any palpable thyroid or tracheal deviation. The chest was symmetrical, with the point of maximal impulse to the right of the left midclavicular line. Heart sounds were normal, without murmurs. Lung percussion note, vocal fremitus, tactile fremitus, and breath sounds were normal, without rales. There were no palpable abdominal masses, nor was there any palpable liver, spleen, or abdominal tenderness. The genitalia were that of a normal boy. Some palpable axillary and inguinal lymphadenopathy was noted. There were bilateral leg ulcers over the anterior distal thirds of both tibiae (Fig. 1). They had a punched-out appearance, with raised irregular edges and granulating bases. The ulcer on the right leg measured 1 by 3 cm., and that on the left leg 1 by 1.2 cm. in diameter. There was moderate pain associated with these lesions.

A moist nonstasis sickle-cell preparation was made on blood secured from the pricked finger. The drop of blood was placed on a slide, covered with a cover slip, and sealed with petrolatum.[8] The preparation was read immediately, one and two hours later, and gave a negative result. However, the 24-hour preparation showed a positive reaction for sickling of the red blood cells. The hemogram showed 3,790,000 red blood cells, 12.6 gm. (88%) hemoglobin content, color index 1.2, 8,550 white blood cells, with a differential count of 46% polymorphonuclears, 2% nonsegment, 47% lymphocytes, 4% monocytes, and 1% eosinophiles. The hematocrit reading was found to be 32, and the nonstasis sedimentation rate was 9 mm. in one hour. The icteric index was 17.0. VDRL and cardiolipin Kolmer test were negative. Urinalysis revealed clear straw-colored urine, with a specific gravity of 1.016. The urine was negative for albumin and

6. Herrick, J. B.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch. Int. Med. **6**:517-521 (Nov.) 1910.

7. Diggs,[1a] Hahn,[1b] Huck,[1c] Sydenstricker, V. P.: Sickle Cell Anemia, South. M. J. **17**:177-183 (March) 1924.

8. Diggs, L. W., and Pettit, V. D.: A Comparison of Methods Used in the Detection of the Sickle-Cell Trait, J. Lab. & Clin. Med. **25**:1106-1111 (July) 1940.

Fig. 1.—Appearance of chronic sicklemia anterior tibial leg ulcers before therapy.

Fig. 2.—Appearance of chronic sicklemia anterior tibial leg ulcers after two weeks of cortisone therapy.

sugar. The urine bile shake test also gave a negative result. X-ray studies of the skull, lungs, abdomen, tibiae, and fibulae showed a negative picture. The nomogram for the area and transverse diameter of the frontal heart silhouette was within normal limits.[9]

The patient was given cortisone acetate (Cortone, Merck & Company, Inc.), 25 mg. three times a day for three days, two tablets a day for two days, and one tablet a day for a total two weeks' dosage of 500 mg. After two weeks of cortisone therapy the larger ulcer on the right leg had completely healed with the characteristic glossy scar (Fig. 2). The smaller ulcer on the left leg showed considerable regression. While under treatment at the clinic the ulcers were covered only with sterile bandages, but were thought to have been left entirely uncovered by the mother after the child went home. The mother reported that the patient's appetite had improved, and that he had gained weight while he was receiving the therapy. The mother and the three children of the second husband, ages respectively 32, 5, 4 years, and 9 months, were tested for sickle-cell anemia in the manner previously described and all the results were found to be negative. Unfortunately, the first husband could not be traced.

COMMENT

Cornbleet [10] recently described complete spontaneous healing of a chronic sickle-cell-anemia ulcer of two years' duration with the onset of pregnancy. Another recent article by Sass [11] described the beneficial effects of cortisone and corticotropin (ACTH) on sickle-cell anemia and concluded that they both had a place in the treatment of sickle-cell anemia. This article describes the effects of cortisone on chronic leg ulcers of four months' duration in a case of sicklemia in which no previous therapy had been of any value.

SUMMARY

One case of chronic sicklemia leg ulcers in which benefits was obtained with cortisone therapy is described.

9. Ehrenpreis, B., and Schwinger, H. N.: Sickle Cell Anemia, Am. J. Roentgenol. **68**:28-36 (July) 1952.

10. Cornbleet, T.: Spontaneous Healing of Sickle Cell Anemia Ulcer in Pregnancy, J. A. M. A. **148**:1025-1026 (March 22) 1952.

11. Sass, M.: ACTH and Cortisone in the Treatment of Sickle-Cell Anemia, New England J. Med. **246**:583-584 (April 10) 1952.

METHOD OF STAINING FUNGI IN CUTANEOUS MATERIAL AFTER CLEARING WITH POTASSIUM HYDROXIDE

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At times it appears desirable to preserve a representative or unusual specimen of mycotic tissue after it has been cleared and examined in potassium hydroxide, be it for demonstration, reference, or further study. In the case of material infected with the common ringworm fungi the slide is easily preserved by the addition of glycerin.[1] Scales infected with Malassezia furfur (tinea versicolor), or material showing Candida albicans in direct examination, are, however,

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman), and the Skin and Cancer Unit of the New York University Hospital.

1. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Ed. 3, Chicago, Year Book Publishers, Inc., 1948.

more perishable. The fungous elements disintegrate within a short time after clearing and addition of glycerin. In such cases, permanent preparations are usually obtained by staining the material directly by one or the other of various methods,[2] without prior examination in potassium hydroxide.

Hoffmann described a method of staining fungus-containing tissue with azure-eosin-glycerin after clearing the material in potassium hydroxide.[3]

Fig. 1.—M. furfur in scale from tinea versicolor, stained with lactophenol-cotton blue after clearing in potassium hydroxide.

2. (*a*) Muskatblit, E.: Staining of Fungi in Scales and Hairs: Method of Staining with Polychrome Methylene Blue, Arch. Dermat. & Syph. **59**:236, 1949. (*b*) Kligman, A. M.; Pillsbury, D. M., and Mescon, H.: Improved Technique for Diagnosing Ringworm Infections and Moniliasis, J. A. M. A. **146**:1563, 1951. (*c*) Gordon, M. A.: Rapid Permanent Staining and Mounting of Skin Scrapings and Hair, A. M. A. Arch. Dermat. & Syph. **63**:343, 1951. (*d*) Chermisirivathana, S.: A Rapid Method of Staining for Fungus and Monilial Infections, J. Invest. Dermat. **19**:7, 1952.

3. Hoffmann, E.: Einfache Dauerfärbung von Hautpilzen und Mikroorganismen mit Azureosinglycerin, Klin. Wchnschr. **17**:1622, 1938.

Scrapings of infected skin and nails, as well as hairs, may be stained by any desired method after clearing if the alkali on the slide has been neutralized by a suitable acid. The following procedure is recommended:

1. Clear material in 10% potassium hydroxide for 5 to 30 minutes, or longer, according to the thickness of the specimen. The material should not be too "soupy" after clearing.

2. Draw off excess alkali with filter paper.

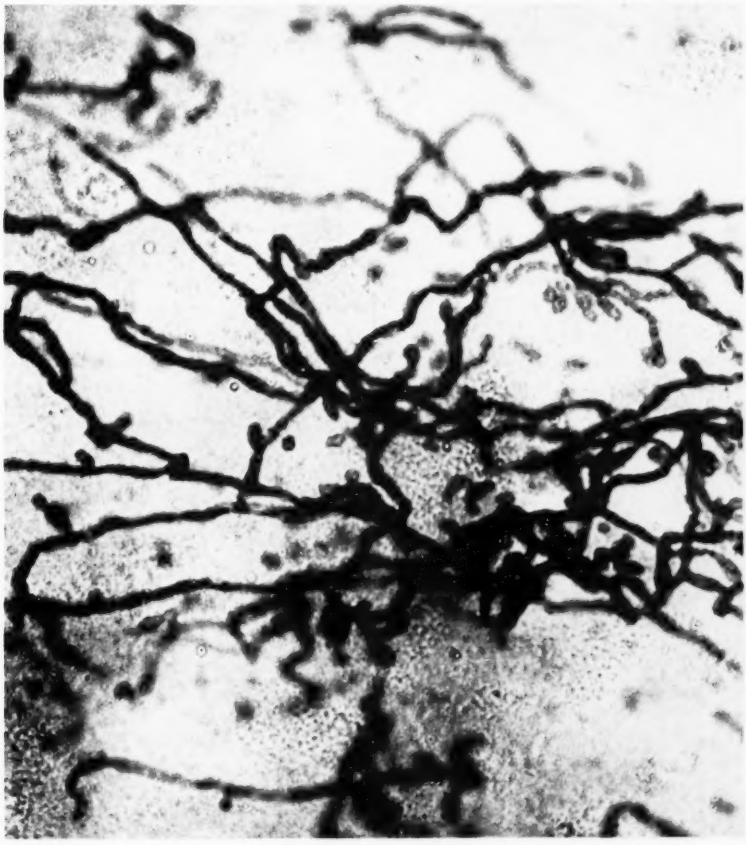

Fig. 2.—Candida albicans in scale from erosio interdigitalis stained by the Hotchkiss-McManus method after clearing in potassium hydroxide.

3. Cover with 5% to 10% lactic acid. Let stand until the pH is acidic all over the area covered—about 3 minutes. If necessary, check with indicator paper of the Hydrion type; the final pH should be 3 to 5.

4. Draw off excess acid with filter paper.

At this point the material may be stained with lactophenol-cotton blue for 5 to 30 minutes, according to the thickness of the specimen. Excess fluid is drawn off with filter paper, a cover glass is applied, and the edges of the cover glass are sealed after a suitable drying period.

If it is desired to stain the material by the Hotchkiss-McManus method, which is somewhat more laborious but which results in better-looking specimens, the above procedure should be followed up to and including step 4. Then—

5. Cover specimen with several drops of 95% alcohol. Let dry several hours. Usually the material will then adhere well to the slide, so that it can be stained without further manipulations. However, if the material is too loose, it should be transferred to an albuminated slide, which necessitates another drying period of several hours.

6. Stain by the Hotchkiss-McManus method.[2b]

Figures 1 and 2 show scales of tinea versicolor and moniliasis, respectively, cleared and stained by the above method.

SUMMARY

A method is described by which fungi in scales, nails, and hairs may be stained by any desired method after direct examination in potassium hydroxide.

146 Fulton St. (2) (C. L. T.).

55 West 42nd St. (36) (E. M.).

USE OF DUPLAST IN RADIATION THERAPY

J. W. CALVERT, M.D.
BLUEFIELD, W. VA.

I experienced considerable difficulty in holding my lead shields in place when close shielding was desired. Duplast,[1] a double-coated Elastoplast which is made of rubber, resins, zinc oxide, and wool fat, was used. The advantage of having adhesive on both surfaces proved satisfactory for the purpose desired; namely, with one adhesive surface pasted to the skin and the other to the shield, it was found that the shields would remain stationary and even, on occasion, the edges of the shield outlining the area of exposure could be held in close apposition to the skin. This proved especially advantageous around uneven surfaces, such as around the eyes, ears, and nose. The same preparation was also used with both the radium plaques and the radium moulds. If filtration was used, one layer of the Duplast was placed between the skin and the filter and another between the filter and the plaque or mould. If filtration was not used, one layer only was used and that was between the plaque mould and the skin. It helped materially in holding these in position, although adhesive was also used over them. It was also found that this preparation could be used to advantage between filters or shields.

The filtration furnished by Duplast was of such a minor nature that it was ignored as an added factor in the calculation of the final amount of filtration in all cases, except where the added distance was important (such as with the radium plaque).

1. Duplast is a trade name of Duke Laboratories, Inc., Stamford, Conn.

TINEA CAPITIS AND CORPORIS IN AN INFANT FOUR WEEKS OLD

EUGENE S. BERESTON, M.D.
AND
HARRY M. ROBINSON Jr., M.D.
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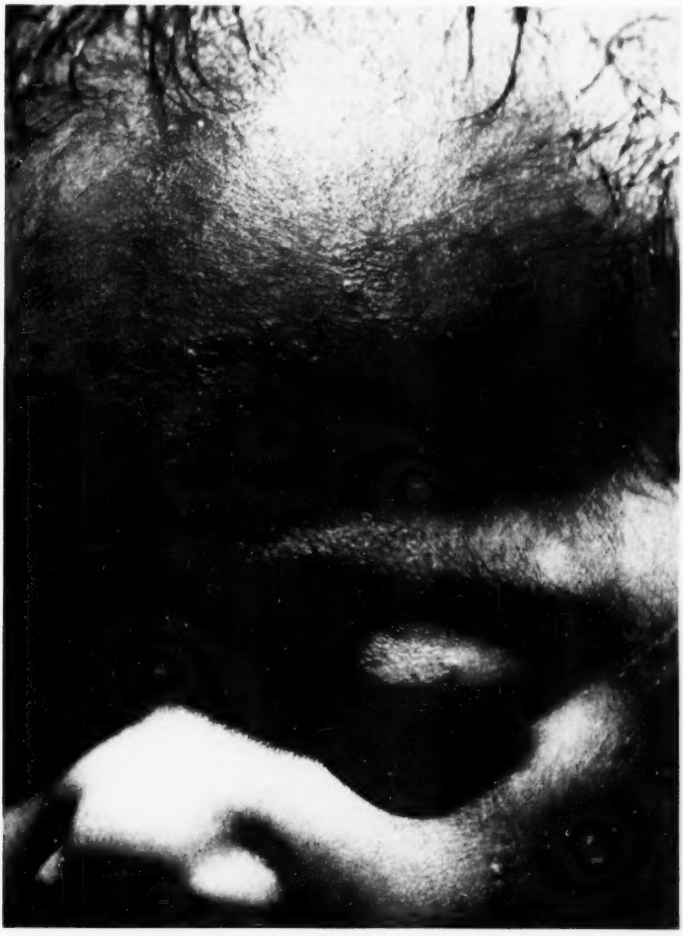
Recently, a 4-week-old Negro infant boy was seen in the skin clinic with several 2 to 3 cm. circinate and annular lesions on the forehead (Fig. 1). These lesions were clear in the center and spreading peripherally. On the frontal, parietal, and occipital regions of the scalp were scattered small scaling areas with broken-off hairs. Typical greenish fluorescence was noted when the lesions were exposed to the Wood light. Scrapings from the skin examined in 20% KOH showed positive results, and cultures of the skin and hairs on Sabouraud media produced Microsporum audouini. Another child, a cousin of the baby, had tinea capitis and was living

in the same house. The mother noticed the appearance of the lesions on the scalp and forehead of the baby two days before coming to the clinic. Perusal of the literature[1] discloses that the youngest patients with tinea capitis caused by M. audouini whose cases are on record were at least one year old. Therefore, we believe that this patient is the youngest patient with M. audouini infection of the scalp yet reported.



Tinea capitis in a 4-week-old infant.

1. Lewis, G. M.; Hopper, M. E., and Reiss, F.: Ringworm of the Scalp: Clinical Data on Recent Cases; Experiences with Local Endocrine Therapy, J. A. M. A. **132**:62, 1946. Schwartz, L., and others: Control of Ringworm of Scalp Among School Children, ibid. 58, 1946. Stritzler, C.; Fishman, I. M., and Laurens, S.: Treatment of Superficial Fungus Infections with a New Antifungal Agent, Tr. New York Acad. Sc. **13**:31, 1950. Edelson, E.; Craster, C., and Haskin, A.: Evaluation of a New Drug for Topical Therapy of Tinea Capitis, A. M. A. Arch. Dermat. & Syph. **64**:444, 1951. Sullivan, M., and Bereston, E. S.: A Study of Topical Therapy in Tinea Capitis, J. Invest. Dermat. **19**:175, 1952.

ECZEMATOUS HYPERSENSITIVITY TO COAL TAR

Report of Three Cases

CLAUDIA R. SIMON, M.D.
AND
ROBERT BRANDT, M.D.
CINCINNATI

Allergic eczematous dermatitis due to coal tar occurs infrequently. Ross [1] observed 170 tar and pitch workers over a 12-year period and reported only six such cases. Chmel [2] described keratocystomatosis of the dorsum of the hand which occurred after therapeutic application of coal tar. A patch test with 5% coal tar gave a positive reaction.

The following are three case reports of hypersensitivity to coal tar which was used for therapeutic purposes. In two cases, an attempt has been made to trace the sensitivity-producing factor (allergen?) to some of the fractions of the tar, and a comparison with shale oil, a related substance, was undertaken.

REPORT OF CASES

CASE 1.—V. S., a 60-year-old white housewife, had a history of psoriasis and superimposed neurodermatitis of five years' duration. A hypersensitivity to coal tar was first suspected by Dr. Robert R. Kierland [3] at the Mayo Clinic, in 1949, when an acute dermatitis developed following topical coal tar therapy of her lesions. He reported to Dr. Leon Goldman that he had obtained positive reactions to patch tests with 5% colloidal crude coal tar (Zetar) in Qualatum (a compound containing petrolatum and fatty acid esters), pine tar in zinc oxide ointment, and 15% juniper tar (Cade oil) in zinc oxide ointment. The patient improved with other bland topical therapies.

Between 1949 and 1952, several exacerbations of the psoriatic and neurodermatic lesions occurred, but temporary improvement was obtained with x-ray therapy, cortisone (Cortone), and bland topical medication.

In April, 1952, the lesions recurred with marked severity, and the patient was first seen here. Because of the history of coal tar sensitivity, a patch test with 2% crude coal tar in an oxycholesterol-petrolatum ointment base (Aquaphor) was applied and gave a positive reaction with vesiculation in 24 hours. A control patch test with the oxycholesterol-petrolatum ointment base alone gave a negative result.

With bland therapies and occlusive bandages, the psoriasis and neurodermatitis subsided.

CASE 2.—M. M., a 64-year-old white housewife, gave a history of varicose veins and stasis dermatitis of the right leg of 30 years' duration. She had been treated with x-ray and bland topical therapy, with temporary improvement.

On Oct. 16, 1952, she was first seen in the outpatient dispensary of the department of dermatology and syphilology and presented erythematous scaly lesions of the right lower leg. Five per cent crude coal tar in petrolatum was prescribed. Several hours after application of the ointment a marked burning sensation was noted at the treated site, and the medication had to be removed. The patient was seen again on Oct. 22, when she had to be hospitalized because of the development of intense erythema, edema, and serous exudate of the right lower leg.

A patch test with 3% crude coal tar in petrolatum was applied and there was positive reaction, with erythema and edema occurring within 48 hours. A control patch test with petrolatum gave a negative result.

CASE 3.—A. W., a 69-year-old white woman, had psoriasis and neurodermatitis, which flared up after tar ointment therapy. She gave a history of a positive reaction to a patch test to tar

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati, Dr. Leon Goldman, Director.

1. Ross, P.: Occupational Skin Lesions Due to Pitch and Tar, Brit. M. J. **2**:369-374 (Aug. 21) 1948.

2. Chmel, L.: Keratocystomatosis (Melczer) Based on Hypersensitivity to Coal Tar, Acta dermat.-venereol. **29**:476-487, 1949.

3. Personal communication to Dr. Leon Goldman.

obtained previously by Dr. Jonathan Forman, Columbus, Ohio. She was given a patch test to tar ointment by Dr. Leon Goldman, and an eczematous reaction was obtained in 48 hours.

Detailed patch testing could not be carried out with this patient because of her out-of-town residency and her lack of cooperation.

As in Cases 1 and 2 there had been positive reactions to patch tests with crude coal tar, it was decided to give the patients patch tests with some of the fractions of coal tar which are mostly mixtures of aromatic compounds. The following is a brief classification of the five main fractions obtained when coal tar is distilled: (1) light oil, which is collected until the temperature of the tar reaches 170 C. and which contains mostly benzene, xylene, and toluene; (2) middle oil, 170-230 C. which contains mostly naphthalene, phenol, pyridine, and quinoline; (3) heavy oil, 230-270 C., which contains mostly phenol, naphthalene, and anthracene; (4) anthracene oil, 270 C. upward, which contains anthracene and phenanthrene; (5) pitch, the residue in the still.[4]

The results of patch tests with individual constituents of these fractions and with a 10% synthetic tar are described in Table 1.

As can be seen, none of these main constituents of coal tar elicited a reaction, although the concentration with which the testing was done was higher than the percentage content of these

TABLE 1.—*Results of Patch Tests with Aromatic Fractions of Coal Tar*

Material	Vehicle	Concentration, %	Results	
			Case 1	Case 2
Benzene	Mineral oil	50	Neg.	Neg.
Xylene	Mineral oil	50	Neg.	Neg.
Toluene	Mineral oil	50	Neg.	Neg.
Phenol	Water	2	Neg.	Neg.
Pyridine	Water	50	Neg.	Neg.
Quinoline	Alcohol	50	Neg.	Neg.
Anthracene powder	.....	100	Neg.	Neg.
Phenanthrene powder	.....	100	Neg.	Neg.
Synthetic tar*	Alcohol	10	Neg.	Neg.

* Manufactured by the Benet Drug Corporation, Cincinnati, and consisting of anthracene, 1.10; naphthalene, 10.20; phenanthrene, 4.00; carbazole, 2.30; picoline, pyridine, quinoline, 0.58 of each; phenol, 0.70; cresol, 0.70, with the addition of petrolatum, 100.00.

substances in the natural whole tar. This points to the fact that we cannot, by mixing the known constituents in appropriate proportion, obtain a product identical with the tar before fractional distillation. It also explains why "synthetic" coal tar is not as effective therapeutically as the crude one.

Because of our inability to determine directly the substance or mixtures of substances responsible for the hypersensitivity, we gave our patients tests with the Colorado shale oil, which is extensively used in our department for therapeutic purposes.[5] As shale oil partly resembles, partly differs from coal tar, it was hoped that the result might help to narrow the number of agents that have to be considered as possible causes of hypersensitivity.

Shale is a mineral formed by sedimentation and encloses organic material of plant or animal origin. When shale is destructively distilled, shale oil is produced. The patch-test results with shale oil are described in Table 2. Patch tests of the patients with all bases used in this experiment gave negative results.

If shale oil is subjected to increased temperature, it can, similarly to tar, be divided into fractions of different boiling points. The first such fraction produced is the naphtha fraction, which

4. Ray, F. E.: Textbook of Organic Chemistry, Philadelphia, J. B. Lippincott Company, 1941, pp. 367-369.

5. Brandt, R., and Dexter, H.: Some Investigative Studies on the Use of Colorado Shale Oil in Dermatological Therapy: A Preliminary Report, J. Invest. Dermat. **15**:163-164 (Sept.) 1950; Investigative Studies on Colorado Shale Oil, ibid. **19**:409-421 (Dec.) 1952.

boils below 200 C. The next fraction, light distillate, is collected between 200-315 C. The heavy distillate is collected between 315-415 C. What remains behind is the residuum. If this residuum is heated to an even higher temperature it cracks, i. e., it is broken up into lower compounds. However, some of these simpler constituents unite again and are re-formed into higher aromatic

TABLE 2.—*Results of Patch Tests with Shale Oil*

Case	Material	Vehicle	Concentration, %	Result
1	Shale oil	Neobase*	10	Pos.
2	Shale oil	Zinc oxide paste†	10	Pos.
2	Shale oil	Petrolatum	3	Pos.

* Oil-in-water emulsion base of the washable types.
† Lassar's plain zinc paste.

TABLE 3.—*Results of Patch Tests with Fractions of Shale Oil*

Material	Concentration, %	Results	
		Case 1	Case 2
Light distillate	100	Neg.	Neg.
Heavy distillate	100	Neg.	Pos.
Uncracked residuum	100	Neg.	Neg.
Cracked residuum	100	Pos.	Neg.

compounds. The results of patch tests with these fractions are described in Table 3. The substances mentioned in Table 3 were not found to be irritating in normal control persons. The lowest boiling naphtha fraction, a primary irritant, was not tested.

SUMMARY

Three cases of allergic eczematous dermatitis due to crude coal tar are presented. Positive reactions to patch tests with the tar were obtained in each patient. Detailed patch testing was carried out in two of the patients. The common aromatic fractions of coal tar gave negative results. Both patients had positive reactions to patch tests with shale oil. When the fractions of shale oil were tested, cracked residuum produced a positive patch-test reaction in the first case, and the heavy distillate test gave a positive reaction in the second case.

As the primary irritation decreases with increasing boiling point, while the content of higher aromatics increases, the latter may be suspected as the cause of the hypersensitivity.

CONIZATION TREATMENT OF INSECT-BITE GRANULOMA

CAPTAIN E. RANDOLPH TRICE
MEDICAL CORPS, UNITED STATES ARMY

Chronic nodular cutaneous granulomas resulting from persistent local reactions to arthropod bites are well recognized. Their clinicopathologic characteristics have been clearly described.[1] In the majority of cases, spontaneous resolution occurs and no definitive therapy is required,

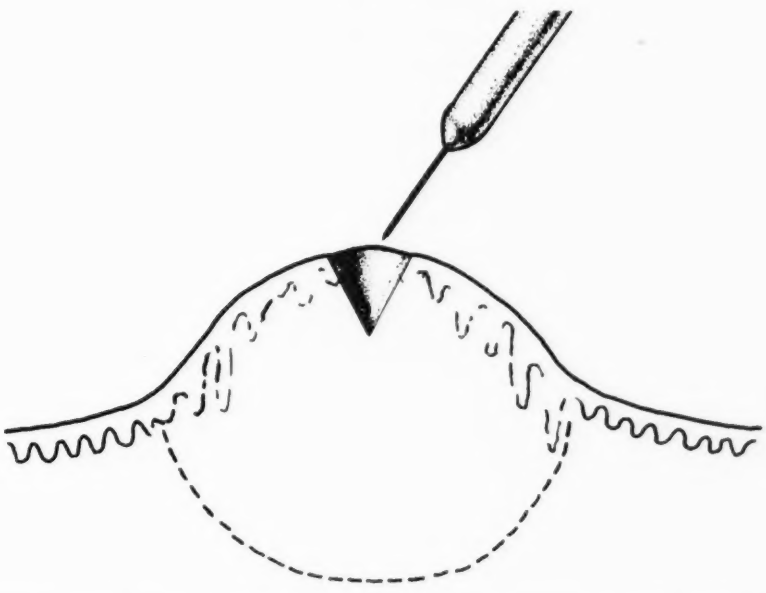
From the Dermatology and Syphilology Section, Medical Service, Walter Reed Army Hospital, Washington, D. C.

1. (*a*) Allen, A. C.: Persistent "Insect Bites" (Dermal Eosinophilic Granulomas) Simulating Lymphoblastomas, Histiocytoses, and Squamous Cell Carcinomas, Am. J. Path. **24**:367 (March) 1948. (*b*) Goldman, L.; Johnson, P., and Ramsey, J.: The Insect Bite Reaction: The Mechanism, J. Invest. Dermat. **18**:403 (May) 1952. (*c*) Goldman, L.; Rockwell, E., and Richfield, D. F.: Histopathological Studies on Cutaneous Reactions to the Bites of Various Arthropods, Am. J. Trop. Med. **1**:514 (May) 1952.

but in rare instances nodular lesions may persist for months or years and may exhibit progressive enlargement. Allen [1a] attributes this response to a stimulating agent from the arthropod or its venom which maintains its activity over many months. Goldman and his associates [1b,c] have demonstrated bits of "cuticular" material in the upper dermis in histopathologic sections of early lesions and suggest that this material, or a similar retained substance, stimulates the chronic granulomatous reaction. If this hypothesis can be accepted, it would appear that removal of that portion of the nodule containing the offending agent should be followed by resolution of the remaining portion of the lesion. This method was used successfully in the treatment of the following patient.

REPORT OF A CASE

A 58-year-old white officer was seen in August, 1951, because of three nodular lesions which had been present on the trunk for four months. The lesions had developed at sites from which ticks had been removed and had enlarged slowly but progressively. They were firm, oval,



Schematic representation, in cross section, of the conization treatment in tick-bite granuloma

dome-shaped nodules with minute central necrotic ulcerations and 1 to 2 cm. in diameter. The clinical impression of tick-bite granuloma was confirmed by the histopathologic finding of extensive granulomatous inflammation in the dermis, characterized by a polymorphous perivascular infiltrate of lymphocytes, eosinophilic leucocytes, plasma cells, and histiocytes. Slight pseudoepitheliomatous hyperplasia was present in the overlying epidermis.

Material for histopathologic examination was removed from the centers of two of the larger nodules by 6 mm. biopsy punches. The base and sides of the biopsy sites were electrodesiccated lightly for hemostasis. Bacitracin ointment was applied twice daily for the next several days. When the patient returned seven days later, the two lesions from which biopsies had been taken had regressed 50%.

Because of the rapid involution after conization of the two larger lesions, it was decided that the remaining lesion should be treated by simple conization of the central portion of the nodule with electrocutting current (Fig.). In two weeks all three lesions had resolved. Except for small flat soft scars at the treatment sites, there was no residual evidence of the lesions.

Only occasional references to the treatment of insect-bite granuloma have appeared, although irradiation, local destructive measures, and surgical excision have been used. The conization method offers the advantages of simplicity, rapid response, and minimal scarring. Since spontaneous resolution may occur, it would seem wise to reserve this procedure for lesions which are large and of long duration.

Osaka Army Hospital, 8009th A. U., APO 1007, c/o Postmaster, San Francisco.

POIKILODERMATOMYOSITIS WITH CALCINOSIS CUTIS

FLAVIANO SILVA, M.D.
ADRIANO DE AZEVEDO PONDÉ, M.D.
AND
FRANCISCO LICHTENBERG, M.D.
BAHÍA, BRAZIL

Among the known variants of dermatomyositis there is a form in which the cutaneous and muscular alterations are accompanied by calcium deposits. One such case was recently observed by us, and the patient was treated with corticotropin (adrenocorticotropic hormone), which brought on temporary improvement of symptoms.

REPORT OF A CASE

A 17-year-old white Brazilian-born girl was first seen on April 2, 1951, complaining of generalized dermatitis and muscular and articular pains. Four years previously she had noticed a generalized patchy pigment disorder and a nonitching facial rash, which had persisted, with partial remissions. In October, 1947, she noticed muscular and articular pains, with redness and swelling of the larger joints. During the preceding two years painful periarticular nodules had appeared, which subsequently began discharging a chalky substance. Since May, 1949, knee movements had become reduced, and on admission she was unable to walk. Physical examination revealed an emaciated young woman lying on her back with both legs in semiflexion. Marked muscular atrophy was noted, especially in the legs. Movements were slow, hesitant, and difficult. The skin lesions consisted of diffuse erythema and telangiectasis over the nose and malar regions; partially confluent pigment spots on the forehead, cheeks, chin, ears, retroarticular regions, and neck, and similar, but larger, spots mixed with depigmented areas on the back, anterior chest wall, and abdomen. The skin of the hands and feet was atrophic and dry, especially in areas overlying articulations. On palpation, one could feel innumerable tiny hard nodules, mainly along the flexor tendons of the legs and arms, and in each axilla. Some of the nodules were ulcerated and discharging a chalk-like substance. The muscles of the extremities were hard and stiff, and their tendons appeared retracted. Active movements were reduced, and the passive movements were painless.

The blood cell count and values for blood protein, cholesterol, urea, creatinine, and sugar were within normal limits, and the Wassermann, Kahn, and Kline reactions were negative.

The basal metabolic rate was +12%. The tuberculin skin test gave a negative result in a 1:1,000 dilution and a positive reaction in a 1:100 dilution. The sedimentation rate was 77 mm. in one hour. The feces revealed Ascaris lumbricoides, Ancylostoma duodenale, and Schistosoma mansoni. The urinary creatine was 160 mg. per 100 cc. and the urinary creatinine 960 mg. The blood potassium was 25 mg. per 100 cc.; blood calcium, 11.4 mg.; blood phosphorus, 4.5 mg. %, and alkaline phosphatase, 3.8 Bodansky units.

Determination of the 17-ketosteroid hormones showed 1.3 mg. in 24 hours. Electrocardiograms and routine chest and abdominal x-ray examinations gave essentially normal findings. An x-ray study of the skeleton revealed calcium deposits around articulations and tendons, marked osteoporosis of the long bones and pelvis, and retarded bone development of the hands. Biopsy of the skin of the retroauricular region, popliteal fossae, and pectoral muscle gave results which were reported as being compatible with the clinical diagnosis of poikilodermatomyositis with calcinosis cutis. Muscle changes were typical of an advanced chronic phase of the disease.

From the University of Bahía.

Corticotropin (ACTH)[1] was administered, 25 mg. every six hours. The articular pains improved rapidly, and 10 days thereafter the patient was able to walk when aided. When a total dose of 4.015 gm. had been administered, the corticotropin therapy was withdrawn. Five days after, the articular pains reappeared, and no further improvement was obtained.

COMMENT

The association of dermatomyositis with calcinosis is found in a considerable number of cases. This particular form may be differentiated from (*a*) a localized reticular pigmented poikiloderma of the face and neck, (*b*) generalized poikiloderma, (*c*) poikilodermatomyositis, and (*d*) poikilodermatomyositis with calcareous deposits.

In the case reported the mechanism of the association has never been elucidated. X-ray examinations of the skeleton revealed marked osteoporosis, while blood calcium and phosphorus, as well as alkaline phosphatase, were within normal limits. Whether the osteoporosis was caused by prolonged immobilization or by other factors is a matter of conjecture.

Corticotropin [1] therapy was prescribed since this disease was far advanced on admission and there was no hope of influencing fibrotic scarring and calcium deposits by any other treatment available. It seems significant, however, that the hormone brought on a remission of muscular and articular pains. The articular mobility improved as it might have done in a case of rheumatoid arthritis, although the response was far less dramatic. One recalls that Freund and associates have described inflammatory and fibrotic foci in muscles in cases of rheumatoid arthritis. In our case, the analogy with rheumatoid arthritis was further emphasized by the history of articular swelling.

It is hoped that earlier manifestations of dermatomyositis may respond to the hormone treatment in a more satisfactory way.

SUMMARY

Corticotropin (ACTH) proved effective in a patient with poikilodermatomyositis with calcinosis cutis; improvement became evident soon after the onset of the therapy. After discontinuance of the treatment there was recurrence of the symptoms.

1. The corticotropin (ACTH) was supplied by F. Caldeira Algodoal, Medical Director, E. R. Squibb & Sons in Brazil.

FORMATION OF MILIA FOLLOWING ABRASIVE TREATMENT FOR POSTACNE SCARRING

SAMUEL MONASH, M.D.
AND
RAFAEL M. RIVERA, M.D.
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Postacne scarring has been treated lately by mechanical abrasion of the affected areas either with sandpaper or with revolving metallic brushes. The purpose of the treatment is to lower the level of the skin to the base of the scar, resulting in a smoother surface. The treatment is very effective in most cases.

We have, however, observed an unexpected sequela in a number of patients treated with a revolving metal brush, namely, the formation of many milia on the treated areas. This did not occur after the first treatment in any patient. However, in about 25% of the patients treated more than once, milia formed about two months after the second or third treatment. They were removed in the usual manner.

There are two possibilities to account for the formation of milia in these patients: (1) Some follicles are closed by the abrasive action of the brush, or/and (2) small bits of epithelium are imbedded in the skin during the procedure.

2 E. 54th St. (Dr. Monash).

From the Department of Dermatology, New York Medical College, Flower and Fifth Avenue Hospitals; Dr. E. F. Traub, Director.

LOCALIZED CONGENITAL ABSENCE OF THE SKIN

LEON GOLDMAN, M.D.
CINCINNATI

Among the rare types of congenital abnormalities of the skin is the actual absence of the skin at birth. This abnormality may include various degrees of involvement, such as just the skin itself, the skin plus subcutaneous tissue, and, finally, even muscle. The commonest site is reported to be the vertex of the head.[1] Extensive scarring may follow. The cause is unknown, but it is not believed that adhesions between the body surface and the amnion are responsible. It is of interest, then, to record the observations on one such case observed shortly after birth and then seven years later.

The child, a white infant boy, was seen shortly after birth, in 1945, at which time two large raw, denuded areas were present on the sides of the chest and the upper abdomen. There was no evidence of trauma or forceps delivery nor any report of abnormality of the placenta. Delivery was normal and spontaneous, and the child was full term, birth weight, 5 lb. 11 oz. (2,580 gm.). On the right side of the chest below the costal margin was a large, 6 by 8 cm., denuded area, without an indurated border and with a glistening red base. The subcutaneous tissue appeared to be absent in this area. There were islands of epithelium in this ulcer. On

Localized congenital absence of skin and subcutaneous tissue shortly after birth on the left side of the body. There had already (1945) been extensive spontaneous scarring.

the left side there was a circular raw, denuded area of approximately the same general diameter, with an area of normal skin in the center. Definite scarring was already visible about both areas. There were also bilateral clubbed feet and some clubbing of the hands, suspected bilateral congenital dislocation of the hips, and extensive capillary type of hemangioma of the nose and upper lip. There was no history of consanguinity or hereditary clubbing. The mother was 36 years old, with one previous normal pregnancy with a normal child. An ointment containing hemin-penicillin [2] was used as topical therapy. Gradually, both areas became scarred over.

The child was seen again in 1952 for a dyshidrosis associated with the wearing of heavy shoes for the clubfeet. The areas on the trunk were all healed over, with the superior portion of the scar on the left side exhibiting an irregular zone of light-brownish hyperpigmentation. About the scar area on the right there has been some difficulty in healing at the center, so that at the present time an ulceration is present. The skin covering appears very thin as if it had been placed right on top of the lower end of the thoracic cage. There is no evidence of contractural deformity. There is definite tension, however, on the ulcerated area on the right, with extreme abduction of the right arm. The child has bilateral clubfeet, with a junctional nevus on the

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati.

1. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, Year Book Publishers, Inc., 1952, p. 529.

2. Liebmann, A. J.; Goldman, L.; Suskind, R., and Friend, F.: Topical Penicillin Therapy: Hemin Penicillin Ointments, Arch. Dermat. & Syph. **57**:733 (April) 1948.

plantar surface of the right foot. There are also bilateral clubhands. There are no other bony abnormalities at present. The hemangioma has disappeared spontaneously. The child is alert, of normal mentality, and attends school.

SUMMARY

A case is reported of bilateral congenital localized absence of the skin and subcutaneous tissue of the trunk, associated with clubbing of the hands and feet. Spontaneous scarring occurred.

THE CENTENARY OF THE HYPODERMIC SYRINGE
1853-1953

SAMUEL J. ZAKON, M.D.
CHICAGO

One hundred years ago a French physician, Charles-Gabriel Pravaz[1] (1791-1853), of Lyons, France, introduced into medical practice the use of the hypodermic syringe. The Pravaz syringe was patterned primarily for the application of ferric chloride to nevi and to aneurysms. The syringe was provided with an external nut working on a thread cut about the piston so that the contained liquid could be extruded drop by drop. Another novel item of this syringe was a slip joint, the needle being of steel and the hub of hard rubber.

Alexander Wood[2] (1817-1884), of Edinburgh, was the first physician to use this hypodermic syringe for the administration of drugs. He injected morphine hydrochloride into patients with intractable neuralgias; in all of them a remarkable rapidity of the effect of the drug was demonstrated. Wood concluded correctly "that in all probability what is true in regard to narcotics would be found equally true in regard to other remedies. That the Pravaz syringe affords a safe, easy, and almost painless method of parenteral therapy."

Great discoveries commonly originate from the fact that a man suddenly grasps the significance of a simple observation or some variation of it that has perhaps been known for years. So it was with Pravaz, who, in search for a method of introducing a liquid coagulant into the lumen of a blood vessel, found it in an inspired variation of the Anel[3] lacrymal syringe, a delicate syringe for the treatment of lacrimal passages.

So let us pause for a moment each time we use a syringe in hypodermic or intravenous therapy and pay tribute to the inventor, the almost forgotten Dr. Charles-Gabriel Pravaz, a man to remember.

Dr. James E. Lebensohn brought Pravaz to my attention.

From the Department of Dermatology, Northwestern University Medical School.

1. Charles-Gabriel Pravaz, Compt. rend. Acad. sc. **236**:88-90, 1953.

2. Wood, A.: On a New Method of Treating Neuralgia by the Direct Application of Opiates to the Pain Points, Edinburgh M. & S. J. **82**:265-281, 1855.

3. Anel, D.: Nouvelle méthode de guérir les fistules lacrimales, ou recuëil de différentes pièces pour et contre, et en faveur de la méme méthode nouvellement inventée, Turin, Zappatte, 1713.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Rudolf L. Baer, M.D., *President*

Henry Silver, M.D., *Secretary*

Jan. 15, 1953

Ragweed Deramatitis Treated by Oral Administration of Acetone Extract of Ragweed: Apparent Clinical Cure and Reversal of Strongly Positive Patch Test to Negativity. Presented by DR. ALEXANDER A. FISHER.

P. B., a man aged 70, was first seen in 1945 with a history of a dermatitis which began in September, 1936. The eruption was most marked on the exposed parts of the body and became perennial with exacerbations in the summer and fall. The patient had a strongly positive patch test to ragweed oleoresin.

In 1946, treatment with ragweed plant oleoresin in corn oil was begun. The preparation is manufactured by the Graham Laboratories, Willow Lane, Dallas, Texas.

The patient was presented before the Society in 1946, 1947, 1948, and 1949 (*Arch. Dermat. & Syph.* **61**:688-690 [April] 1950; **64**:647-648 [Nov.] 1951). The following is a summary in tabular form of the clinical course and patch test reactions of the patient since 1946.

Date	Patch Test	Clinical Appearance	Improvement	Comment
1946	3+	Severe	.....	Oral therapy was begun
1947	3+	Moderate	25%	First complete year of therapy
1948	2+	Mild	50%	Second complete year of therapy
1949	Negative	Clear	100%	Third complete year of therapy
1950	2+	Moderate	25%	Therapy discontinued for several months
1951	Negative	Clear	100%	Therapy resumed for four months
1952	Negative	Clear	100%	Patch test remained negative and skin remained clear in spite of no therapy for over 18 months

A fresh patch test with ragweed oil was performed two days before this presentation. The result was again negative.

DISCUSSION

DR. DAVID BLOOM: Because of the long duration of treatment necessary to clear this eruption, is it not possible that we may be dealing with a spontaneous desensitization?

DR. VICTOR H. WITTEN: I believe that it is unanimously agreed that the results Dr. Fisher has presented tonight are worth while. In general, it can be stated that once allergic contact sensitivity of the skin has been established, it remains essentially unchanged throughout life. There are, however, unpredictable fluctuations as well as instances of diminished sensitivity manifested over the years. This was shown by Wedroff and Delgoff (*Arch. Dermat. u. Syph.* **171**:647-664, 1935), in addition to others, by testing patients sensitized to 2, 4-dinitrochlorobenzene. It was their experience that there was not only a decreased degree of sensitivity in some cases but also a high incidence of spontaneous loss of sensitivity. Hilliard Shair and I (*Ann. Allergy* **7**:32 45 [Jan.-Feb.] 1949) repeatedly patch-tested patients known to be sensitive to various contact allergens, and it was our experience that the degree of sensitivity remained essentially unchanged and, if anything, was increased with the repeated application of the allergen (as demonstrated by using graded dilutions). The negative patch test response in this patient conceivably could be explained by a local nonreactive area. Such areas have been demonstrated for poison ivy by Field and Sulzberger (*J. Allergy* **7**:139-144 [Jan.] 1936).

DR. RUDOLF BAER: This is a most unusual presentation. In the many years in which I have been interested in the problems connected with allergic eczematous contact type sensitivity, I have never observed a patient in whom complete desensitization, as evidenced by a negative patch test reaction, had been deliberately achieved through the administration of

specific extracts. The patient presented tonight by Dr. Fisher and several other patients in this series are the first examples of this phenomenon which I, myself, have been able to observe. As a rule, allergic eczematous sensitivity continues for many years, once it is well established, with only minor fluctuations in the level of sensitivity. However, it is little known that during the early phase of allergic eczematous sensitizations, there is a significant minority of patients in whom desensitization takes place spontaneously, as was shown by Dr. White and myself some years ago. We referred to this phenomenon as "early spontaneous desensitization" (*J. Allergy* **21**:344-348 [July] 1950.)

In the tuberculin type sensitivity, hyposensitization through repeated injections of specific extracts, starting with high dilutions and gradually increasing the concentration, is often followed by a temporary significant lessening sensitivity. However, it seems to be the rule in such cases, soon after this procedure has been discontinued, for the sensitivity to increase again, frequently to the level which was present at the start of the hyposensitization procedure.

In the urticarial type of allergic sensitivity, complete, deliberate desensitization, as a rule, cannot be achieved even after years of hyposensitization procedures. The literature, as well as the opinion of highly competent allergists, indicates that while there is some reduction in sensitivity in some cases, complete desensitization cannot be achieved.

DR. IRWIN I. LUBOWE: When was the patch test last positive?

DR. FRANK F. CROSS: The patient has not worked as a delivery truck operator for the past two years; this may have been a factor in his improvement, inasmuch as his exposure may have been less or none.

DR. PERRY SACHS: I wonder what the results would be in a control series without this therapy observed over a similar period.

DR. ALEXANDER A. FISHER: In answer to Dr. Witten's question about local sensitivity or nonsensitivity to the patch test, I have tested the patient on his back and different areas of the arms and in all sites the tests proved negative. In answer to the question as to whether there is a spontaneous cure in ragweed dermatitis, Dr. Shelmire tells me that he has never observed a patient with ragweed dermatitis that cleared spontaneously. Regarding control cases, I would like to mention several patients who refused or were unable to take the treatment and over a period of three years their patch tests have remained as strongly positive as when they first came to the clinic. On the other hand, patients who are receiving treatment after their third year of therapy show, in their patch tests, definite signs of lessening positivity. As to the question of reactions from the therapy, in only one case did I have to stop treatment entirely, because the oleoresin caused severe abdominal cramps. Occasionally, itching of the rectum occurs, but on cessation of the treatment for one week, the itching subsides and the medication can be resumed. I have also had patients with mild toxic eruptions, but these eruptions subside quickly, and I was always able to continue the medication. As far as poison ivy is concerned, I have observed patients for three years; in contrast to cases of ragweed dermatitis, the oral therapy does not seem to have any effect on the patch test. In other words, the patch tests have remained strongly positive in spite of the oral therapy.

Poikiloderma Atrophicans Vasculare (Jacobi). Presented by DR. ALEXANDER A. FISHER.

Lymphoblastoma. Presented by DR. JOHN GARB and DR. NORMAN B. KANOF.

Adenocarcinoma of the Large Bowel (Metastatic?) and Recurrent Lupus Vulgaris After Cessation of Calciferol Therapy. Presented by DR. JOHN GARB.

Pemphigus Erythematodes (Senear-Usher) with Features Suggestive of Dermatitis Herpetiformis. Presented by DR. FRANCES PASCHER.

Eosinophilic Granuloma of the Face. Presented by DR. DAVID BALLIN.

Neurofibroma. Presented by DR. NATHAN SOBEL.

Gumma of the Tip of the Nose. Epithelioma? Presented by DR. NATHAN SOBEL.

Case for Diagnosis: Factitial Ulcer? Presented by DR. ABRAHAM J. ORFUSS.

Pigmentation of the Face from Freckle Cream. Presented by DR. ALEXANDER A. FISHER.

Erythema Annulare Centrifugum. Dermatitis Artefacta? Presented by DR. ABRAHAM J. ORFUSS.

Method of Patch Testing for Allergic Stomatitis Due to Acrylic Denture Resins. Presented by DR. ALEXANDER A. Fisher.

Monilethrix in Twins. Presented by DR. ABRAHAM J. ORFUSS.

Congenital Fibromata(?) of the Fourth and Fifth Fingers of the Left Hand. Presented by DR. ALEXANDER A. FISHER.

CHICAGO DERMATOLOGICAL SOCIETY

Samuel J. Zakon, M.D., *President*

Irene Neuhauser, M.D., *Secretary*

Feb. 18, 1953

Acute Disseminated Lupus Erythematosus. Presented by Dr. Samuel Bluefarb, Dr. Aaron Goldberg, and (by invitation) Dr. J. F. Sickley.

History.—The patient is a 34-year-old Negro woman. She entered the hospital on Dec. 16, 1952, complaining of chills, fever, and cough. She had apparently been well until about four days before admission to the hospital.

Laboratory findings showed the patient to have 4+ albuminuria and a leucopenia. Peripheral blood and sternal marrow L. E. preparations done on Jan. 2 were negative.

A dermatology consultation was requested on Jan. 2. At that time the only cutaneous manifestation present was a mottled hyperpigmentation of the flexor surfaces of the fingers.

The clinical course remained unchanged, and on Jan. 12 it was noted that there was a "suggestion of a butterfly-type lesion over the bridge of the nose and cheeks." On Jan. 16 it was noted that the face lesions had "become more extensive," and the peripheral L.E. preparation was repeated. This was reported as positive. On Jan. 17 corticotropin (ACTH) therapy was started. The patient responded well, but around Jan. 28 thrombophlebitis of the left leg developed, and this was followed by abscess formation. Because of the latter complication, the corticotropin was discontinued on Feb. 5. Since that time the patient has again complained of weakness, chills, loss of appetite, and fever.

Physical Examination.—At present the patient has slight erythema and moderate hyperpigmentation over the nose, cheeks, forehead, and about the ears. There are also a few areas of hyperpigmentation on the arms. The fingers show a speckled hyperpigmentation.

Other positive findings were a soft systolic murmur at the apex of the heart and a firm tender mass in the left lower quadrant (pelvic inflammatory disease). There were also nodes palpable in the cervical, axillary, inguinal, and epitrochlear regions.

Laboratory Findings.—Laboratory studies revealed the following: urinalysis, 4+ albumin; hemoglobin 64%; red blood cell count 4,310,000; white blood cell count 4,200, with polymorphonuclear leucocytes 66%, neutrophile bands 8%, lymphocytes 16%, monocytes 10%, serology negative; total protein 7.0 gm.; albumin 3.6 gm.; globulin 3.4 gm.; total cholesterol 167 mg.; gamma globulin 2.0%; thymol turbidity 7.8 units; cephalin flocculation 3+; agglutination tests for Salmonella typhosa and brucella negative; L. E. preparation of Jan. 16 positive; chlorides 100 mEq.; sodium 138 mEq.; potassium 17.6 mg.; chest x-ray, "heart and lungs normal."

DISCUSSION

Dr. Stephan Rothman: Tiny red telangiectatic spots on palms and bluish red discoloration periungually are rather characteristic signs of the disease. They can be seen in this case in spite of the dark pigmentation.

Dr. S. M. Bluefarb: I would like to call attention to the thrombosis resulting from corticotropin, which occurs in many patients. Treatment with corticotropin results in an increase in the clotting mechanism. Last year we saw a patient in whom a gangrenous process of one toe developed as a complication of corticotropin therapy.

Dr. Zakon: Could you obviate that by giving small doses intravenously instead of large doses intramuscularly?

Dr. Bluefarb: It is my impression that corticotropin in any form will increase the clotting mechanism.

Pellagra. Presented by Dr. Herbert Rattner, Dr. Harold Rodin, and (by invitation) Dr. J. F. Sickley.

DISCUSSION

Dr. Stephan Epstein, Marshfield, Wis.: This was a very classical case of pellagra; I have not seen such a typical one for a long time. There were all the symptoms, the skin lesions, the gastrointestinal symptoms, the psychosis. The skin lesions were very typical. I would like to

stress one symptom that Jadassohn stressed, follicular plugging of the nasolabial fold, with spine-like keratoses. This patient showed it beautifully. One has to admire the courage of the internist who treated the patient for five days with thiamine hydrochloride only. However, that gave a chance to see the dramatic effect of nicotinic acid (Niacin) therapy. But, as Tom Spies pointed out many years ago, there are more deficiencies found in pellagra, especially thiamine and riboflavin.

One thing that interests me is the relationship of the pellagra to sun sensitivity. There seems little doubt that there is some relationship, but of what nature? We find pellagra in exposed areas. But this light sensitivity in pellagra is so different from other sun sensitivity diseases. In prurigo aestivalis the eruption is located exactly at the sites of exposure. In pellagra the eruption usually extends beyond the exposed areas. Often, also, the nonexposed sites, especially the genital area, are involved. In this patient there are also lesions of the elbows. Furthermore, in most cases of sun sensitivity the eruption occurs around March; in pellagra the disease often starts earlier, in January or before. This patient had symptoms already in October. Experimentally, as far as I remember, one cannot reproduce the lesions of pellagra by exposure to ultraviolet; at least I have never been able to do so.

These are all questions. I know I do not have the answer to them, but I hope someone else does.

DR. H. H. RODIN, South Bend, Ind.: The Department of Dermatology was called in consultation in this case merely for diagnostic purposes. No therapeutic suggestions were made, since from previous experience we have found that the internists resent such advice in medical cases unless specifically requested.

We were able to observe this patient following the administration of thiamine hydrochloride (thiamine chloride) and found her in such deep coma that she appeared dead. The administration of nicotinic acid produced an almost miraculous recovery.

DR. S. M. BLUEFARB: This woman presented one other important sign of pellagra, namely, the pigmentation around the neck, Casal's collar.

Erythema Nodosum (Due to Quinacrine [Atabrine] Hydrochloride?). Presented by DR. JAMES WEBSTER, and (by invitation) DR. BERNARD PASS.

History.—H. C., a 40-year-old Negro woman, has been a patient at Northwestern University Medical School since Nov. 1948. She has had a large erythematous atrophic patch of scarring alopecia on the frontal scalp region for the past six years. There are also a number of atrophic scarred areas on the face which have been present for about four years. The large scalp lesion has constantly shown signs of activity, as manifested by erythema and scaling. Treatment in the past has consisted of administration of bismuth, calciferol, quinine, and liver extract.

The past history revealed that the patient had been treated at the City of Chicago Municipal Tuberculosis Sanitarium as a patient with an active case of tuberculous adenitis involving the left cervical glands. These lesions, according to their reports, have healed. Repeated x-ray examinations of the lungs revealed no evidence of tuberculous infection.

Quinacrine (Atabrine) hydrochloride was administered orally starting Nov. 17, 1952, in dosage of 100 mg. three times a day for two weeks, then 100 mg. twice a day for three weeks, then 100 mg. daily. During the quinacrine hydrochloride management the scalp lesion improved to the degree that there was only spotty erythema. Nine weeks after the first dose of quinacrine hydrochloride the patient complained of having painful nodules on the legs and forearms. Examination revealed a number of erythematous, markedly tender nodules on the right and left forearms and anterior and posterior aspects of the left leg. She had a temperature of 100.4 F.; her ankles were swollen, and she felt quite ill. The administration of quinacrine hydrochloride was stopped, and the patient was placed on acetylsalicylic acid, cool packs, and bed rest. During the next three weeks new painful nodules continued to appear, the old ones becoming painless. There was no ulceration. The febrile symptoms abated, and she felt well.

A biopsy was performed and was reported as consistent with erythema nodosum.

Laboratory Findings.—The laboratory findings were as follows: urinalysis negative; Kahn test negative; white blood cell count 6,500 with 66% polymorphonuclear leucocytes. The chest x-ray was reported as "calcified healed tuberculosis of the left apex with no evidence of activity, and calcified lymph nodes of the left side of the neck." Blood chemistry revealed normal values.

DISCUSSION

DR. GEORGE C. WELLS (by invitation): I was very interested to see the first patient with erythema nodosum. Of course, with an old history of tuberculous glands, one wonders whether this is a drug eruption in its own right or whether the tuberculous process is being activated in some way. It would be unusual for erythema nodosum to appear in an old tuberculous case, but it might be related to changing sensitivity with reactivation of long latent disease.

DR. OTTO STEGMAIER, Davenport, Iowa: I had a patient in whom a case of acute psychosis developed while under quinacrine hydrochloride therapy. On looking up the literature I found, which would explain Dr. Rubin's case, that the quinacrine hydrochloride stains the meninges and some of the brain tissue, and, after quinacrine hydrochloride medication is stopped, the pigmentation disappears.

DR. HAROLD SHELLOW: At the suggestion of Dr. Belisario, I have used vitamin B_{12} in all patients receiving quinacrine hydrochloride and have encountered no toxic effects from the quinacrine hydrochloride. In addition, in my opinion, clinical results appear to be better. The dosage is 25 or 30 γ three times daily.

DR. HAROLD H. RODIN, South Bend, Ind.: Concerning the use of vitamin B_{12} for protection against untoward reaction from quinacrine hydrochloride, I would like to call attention to a recent article in *Science* which suggests a possible antagonism between vitamin B_{12} and quinacrine hydrochloride.

Actinic Dermatitis of Poth. Presented by Dr. A. W. STILLIANS.

History.—Mr. A. G. H., 43 years old, a consultant for industrial relations, was seen and treated for a virus infection in June, 1952, receiving penicillin and some sulfonamide drug for about a month. During July he went fishing and was bitten by some sort of an insect on the right side of the forehead. On consulting Dr. Hedge in August, there was a crusted area 7.5 by 10 mm. surrounded by a red halo 3 mm. wide. It itched only mildly.

After being given 350 r of unfiltered x-rays, limited to the area involved, the crust cleared. Soon after this, several new patches of erythema appeared on the forehead and one on the top of the nose.

Physical Examination.—When seen by me on Nov. 25, 1952, the patient had nine round macules, some of them with a central crust, on the forehead; two on the right temple; one each on the left temple, left cheek, and left side of the tip of the nose. These were all smaller than the original one on the forehead, which was a depressed scar with a central crust over two-thirds of its extent.

The crust had dropped off the nose lesion when first seen by me, leaving a depression surrounded by a slightly elevated rim. Since then crusts have been forming and building up 3 or 4 mm. in thickness.

The patient was given 0.5 gm. sodium thiosulfate intravenously on Nov. 28 and again 1.0 gm. on Dec. 8 and Dec. 15.

Laboratory Findings.—On Nov. 25 the urine was normal, except for 5 mg. albumin, 10 to 15 white blood cells per high-power field. No red color appeared by Wood's light or on standing in sunlight.

Blood studies were reported as follows: hemoglobin 95%; red blood cells 5,180,000; white blood cells 12,500, with lymphocytes 33%, monocytes 4%, eosinophiles 2%, polymorphonuclear neutrophiles 59%, metamyelocytes 2%. Sedimentation rate was 4 mm. in one hour. Kahn test was negative.

A biopsy on Feb. 2, 1953, showed the horny layers much thickened and loose layers with many dark granules penetrating as plugs into the Malpighian layer in places. The granular layer was deficient. There were great acanthosis and considerable round cell infiltrate in the papillary layer.

Pathological diagnosis was senile keratosis.

DISCUSSION

DR. M. R. CARO: I assume that this case represents the same condition that Dr. Poth described as pseudoepitheliomatosis occurring in patients who were exposed to the sun a great deal. Often these lesions disappeared spontaneously when the patient was kept away from the

sun. If this is what Dr. Stillians has in mind, it is not a dermatitis but a form of keratosis. Instead of using radium therapy, such lesions might better be treated by the actual cautery. I should hesitate to use more irradiation in a skin already badly burned.

DR. A. W. STILLIANS: The word dermatitis was used, because I consider it a result of sensitization to light by the sulfonamide drug that was given him in June. I thought, too, that it had a resemblance to hydroa vacciniforme. These lesions came on acutely and caused scarring. If my theory is correct, I expect the lesions to heal spontaneously. He is getting no treatment now, except the daily application of compound benzoin tincture.

Drug Eruption—Antipyrine. Presented by DR. DAVID OMENS and (by invitation) by DR. HAROLD OMENS and DR. STEFAN BIELINSKI.

Dermatitis Medicamentosa. Presented by DR. HERBERT RATTNER, DR. HAROLD RODIN and (by invitation) by DR. STEFAN BIELINSKI.

Lupus Vulgaris? Presented by DR. HERBERT RATTNER, DR. HAROLD RODIN and (by invitation) by DR. STEFAN BIELINSKI.

Fox-Fordyce Disease. Presented by DR. JAMES WEBSTER, DR. STANLEY HUFF and (by invitation) by DR. J. F. SICKLEY.

Sarcoidosis? Presented by DR. DAVID OMENS and (by invitation) by DR. HAROLD OMENS and DR. STEFAN BIELINSKI.

Gouty Diathesis. Presented by DR. SAMUEL BLUEFARB, DR. AARON GOLDBERG and (by invitation) by DR. J. F. SICKLEY.

Lupus Erythematosus? Presented by DR. FRANCIS SENEAR and DR. HOMER E. HARRIS.

Chronic Discoid Lupus Erythematosus Treated with Quinacrine (Atabrine) Hydrochloride. Presented by DR. SAMUEL J. ZAKON.

Lupus Erythematosus (Chronic Discoid). Presented by DR. A. M. BUCHHOLZ.

Morphea-Like Epithelioma. Presented by DR. HAROLD SHELLOW.

Acanthosis Nigricans, Juvenile Type, with Possible Hypercorticoidism. Presented (by invitation) by DR. ALLAN L. LORINCZ and DR. FREDERICK MALKINSON.

Lichen Planus of Oral Mucosa (Acute Exacerbations from Smoking). Presented by DR. STEPHEN ROTHMAN and (by invitation) by DR. JAMES K. TOMPKINS.

Epidermolysis Bullosa (Dystrophic). Presented by DR. H. HAROLD RODIN.

Case for Diagnosis (Persistent Pityriasis Rosea?). Presented by DR. MALCOLM C. SPENCER.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Marion B. Sulzberger, M.D., *Chairman*

Lowry Miller, M.D., *Secretary*

Jan. 6, 1953

Leprosy: Tuberculoid Type, Treated Unsuccessfully with Isoniazid (Nydrazia) and Diplopia Caused by Leprosy. Presented by DR. MAURICE J. COSTELLO.

J. L., a 55-year-old man of Italian birth, has had leprosy about 40 years—since the time he was in Argentina. His condition was first diagnosed and confirmed by biopsy in 1944. Since that time, he has suffered from pain, anesthesia, and hyperesthesia caused by the neuritis so frequently associated with this disease. He is presented to demonstrate the erythema-multiforme-type of lesions on the torso and for suggestions of therapy to relieve the symptoms mentioned above. Every known form of therapy of any rational value has been used, without avail. Histamine test was made on several occasions.

DISCUSSION

DR. GERALD F. MACHACEK: This extremely interesting case of leprosy is similar to one we observed recently at the Vanderbilt Clinic. In the latter case a mere erythema was shown. Only our suspicion led us to the diagnosis of leprosy. I should mention the fact that leprosy is one of the extremely rare conditions in which the fingerprint pattern is changed. I looked carefully at this patient's fingers and discovered that although his thumbs retained their patterns the other digits, with the exception of the index finger of the left hand, showed an obliteration of the patterns.

DR. FREDERICK REISS: I think that this case presented by Dr. Costello is interesting from a diagnostic point of view, but I wish to make a few remarks regarding the treatment also.

In my personal experience isoniazid (Nydrazid) has not been very successful in lepromatous leprosy, and in such cases the sulfone drugs are still far better. The value of isoniazid in tuberculoid leprosy is difficult to appreciate. Another therapeutic problem, which is a rather important one in this type of leprosy, is the polyneuritis. In most instances, large doses of vitamin B_1 are beneficial. The clinical features, of course, are suggestive but not very characteristic of the tuberculoid type. One would expect a more pronounced atrophy in the center of these lesions and, furthermore, the pebbled, granular border which is so characteristic of the tuberculoid type. In addition, in most cases, the peripheral nerves are enlarged, this being not very pronounced in this case. I am sure that the microscopic features are characteristics enough upon which the diagnosis is based, and, of course there is the negative reaction to histamine. I would suggest that instead of isoniazid any of the less toxic sulfones combined with thiamine hydrochloride be used.

DR. ORLANDO CANIZARES: I agree in part with what Dr. Reiss has said. I feel that the sulfone medications do help in the lepromatous type, but in the tuberculoid type their action is sometimes rather uncertain. Patients do improve for a short time, and later improvement stops. The action of the isoniazid derivatives seem to be less certain in cases of tuberculoid leprosy. In many instances they do not seem to help at all. In some cases of the lepromatous type the patient improves somewhat clinically, but the scrapings still show the leprosy bacillus.

DR. MARION B. SULZBERGER: Would you care to say something about the newer antileprosy drug DDS (4,4′ diaminodiphenylsulfone)? Have you had any experience with it?

DR. ORLANDO CANIZARES: I do not have a personal experience with it.

DR. FREDERICK REISS: In regard to your question, the diethyl diamino sulfone is rather toxic. On account of the toxicity one should be rather careful in choosing that particular drug. I think that amongst the sulfone drugs, the least toxic is Sulphetrone (4,4′-bis[gamma-phenyl-N-prophylamino]-diphenylsulfone-tetrasodium sulfone). The mother substance of all sulfone drugs is the diethyl diamino sulfone.

DR. GERALD F. MACHACEK: The prognosis in cases such as this one is good, regardless of therapy. I have observed a number of cases in which the disease appeared to be benign in which, when treatment was given, leprosy reactions of varying degree developed. These leprosy reactions take various forms. There may be cutaneous manifestations, neuritis may develop, and often a uveitis may occur. Specific therapy with concomitant exhibition of cortisone or corticotropin (ACTH) is indicated.

DR. MAURICE COSTELLO: The main purpose of presenting this case was to show the circinate erythema-multiforme-like lesions that this patient presented. He had been seen by physicians in nearly every clinic in New York and most of the time he went to these clinics when he had a generalized eruption associated with a mild degree of fever, and in each instance the diagnosis of erythema multiforme was made, indicating how the disease simulates that condition very strikingly. This man has diplopia. Also, on turning his eyes to the right he sees double, and I thought that if isoniazid was going to be of any value it should have affected favorably that neurologic manifestation, which it did not. If there is any therapy that has ever been used in recent years that has any rational basis in leprosy other than what he has received I should like to know what it is. Glucosulfone (Promin) sodium, sulfone (Diasone) sodium, Promacetin, cortisone, and nearly everything that one can mention has been administered, without the slightest benefit. It has been my experience that in the treatment of leprosy, in the City of New York anyway, one achieves nothing with it. The only possible promising therapeutic effect is from the use of isoniazid or one of those isonicotinic acid derivatives in the lepromatous type.

Sporotrichosis, Lymphangiectatic Type. Presented by DR. ANTHONY C. CIPOLLARO, for DR. JOSEPH L. SINGER (by invitation).

W. B., a white boy, aged 19, has worked for a florist and bulb farm on Long Island for 10 years. In 1945, several companions at work contracted sporotrichosis. About the first of December, 1952, the patient noted a tender nodule on the right calf, which enlarged and ulcerated. Adjacent tender nodules also appeared above the original lesion. At the time of onset, he had been handling soggy salt hay.

When he was first examined on Dec. 18, 1952, a punched-out ulcer measuring 15 by 20 mm. in diameter was noted in the center of the right calf. The base and borders consisted of dusky-red granulation tissue, with a slight serous discharge. Medial and above this ulcer was a chain of shotty tender subcutaneous nodules, each surrounded by a zone of erythema and extending upward to the popliteal space. As time went on, the nodules came closer to the surface, enlarged, and softened. The ulcer has become flatter with therapy. Regional lymph nodes are not enlarged.

The laboratory results were as follows: (*a*) Serosanguineous material aspirated from the granulation tissue in the ulcer grew Sporotrichum schenckii in all tubes of Sabouraud's medium. (*b*) Sporotrichin skin test gave a doubtful result. (*c*) Tissue specimen stained with the Schiff reagent revealed Sporotrichum organisms. (Through cooperation of Dr. R. Benham, Department of Dermatology, College of Physicians and Surgeons of Columbia University.)

Therapy consisted of administration of potassium iodide by mouth.

DISCUSSION

DR. GERALD F. MACHACEK: I happened to see sections of a biopsy from this case, and although the hematoxylin and eosin sections showed only a little abscess around the hair follicles the material stained with the McManus stain did show fungi. It is obvious that the cultures are those of a Sporotrichum.

DR. FREDERICK REISS: Dr. Singer is to be congratulated. He is making a very impressive collection of cases of sporotrichosis. The interesting feature in this case was the source of the infection; to my knowledge these are the only instances in which salted hay was the transmitter of the disease.

DR. TIMOTHY J. RIORDAN: In relation to the hay idea, this is a compensation case. This I think is the second one that Dr. Singer has presented. It so happens that he practices on the other end of Long Island in an area where they raise tulips. In certain seasons of the year the ground is covered with this hay. It might be said too that this now is the fourth case of sporotrichosis reported under the New York State Compensation Act.

DR. J. LOWRY MILLER: Dr. Singer stressed the fact that it is salt hay, not the ordinary meadow hay. That is what they use in covering the plantings.

DR. NATHAN SOBEL: I should only like to say that it is really a mild form of sporotrichosis that we are seeing. It heals quite readily with large doses of potassium iodide.

DR. ANTHONY C. CIPOLLARO: I want to thank you all for the discussion. As you know, I saw this patient for the first time tonight. The patient was brought to this meeting by Dr. Singer, who diagnosed the condition and confirmed the diagnosis by cultural examinations. So far, Dr. Singer has discovered 11 cases of sporotrichosis in the vicinity of Bay Shore, Long Island, during the past four years. Seven of these have already been reported in the *New York State Journal of Medicine*. All the patients were males, all workers engaged in tulip raising, and the boy presented tonight is employed part-time by a tulip raiser and part-time goes to agricultural school on Long Island.

Case for Diagnosis (Lichen Ruber Planus). Presented by DR. TIMOTHY J. RIORDAN and DR. LOUIS V. LUTTENBERGER (by invitation).

L. G., 48 years of age, has had a slowly progressing pruritic skin lesion on the left leg since 1949.

The clinical findings were as follows: On the outer aspect of the lower third of the left leg there was a hand-sized skin lesion consisting of numerous pin-head-sized brown dull reddish papules arranged in circinate and serpiginous fashion, progressing on the periphery and healing in the center with pliable scars. On the medial aspect of the upper part of the left leg there was a coin-sized similar lesion of brownish red color, with lichenified center and a peripheral rim of pin-head-sized slightly scaly papules.

The laboratory findings were as follows: A biopsy done on Nov. 2, 1952, revealed the following findings: The granular layer was prominent; the corium showed moderate parakeratosis.

A dense diffuse infiltration of lymphocytes was found throughout the derma. The fixed tissue cells in the derma increased in number. The serological reactions for syphilis were negative on Aug. 12 and Nov. 12.

The patient received 20 bismuth injections.

DISCUSSION

DR. FRANCES PASCHER: I should like to suggest the diagnosis of necrobiosis lipoidica; the unilateral distribution, the central yellow discoloration, along with the telangiectatic and atrophic changes and the absence of itching are points in favor of the latter diagnosis. An annular papular border is not unusual in necrobiosis, particularly in the early stages.

DR. JACK WOLF: The patient presents typical annular lichen planus of the penis. Under the circumstances, I think that the eruption on the leg, while not absolutely characteristic, is nevertheless that of lichen planus.

DR. H. GOODMAN: I think that the alleged lesion was only on the right leg. In the textbooks of 1860 this was labeled "gumma."

DR. PAUL GROSS: I agree with the diagnosis of lichen planus.

DR. NATHAN SOBEL: I will agree that when one looks at the lower lesion, the large lesion, that it has a serpiginous outline so that it suggests tertiary syphilis from the distance; however, when one looks at it more closely one sees that there is not any nodular type of lesion of the kind that one expects in syphilis, and the upper lesion certainly had very typical lichen planus papules around the border. I did not look at the penile lesions.

DR. ARTHUR B. HYMAN: A biopsy report should answer the problem of necrobiosis lipoidica versus lichen planus, without further discussion.

DR. MARION B. SULZBERGER: Would you like to have the biopsy findings read?

DR. TIMOTHY J. RIORDAN: The granular layer is prominent, and the corium shows moderate parakeratosis. A dense diffuse infiltration of lymphocytes is found throughout the dermis. The fixed tissue cells in the dermis increased in number. It is in the interstitial cells.

DR. ARTHUR B. HYMAN: Then all the discussion is futile.

DR. MARION B. SULZBERGER: Futile in what direction?

DR. ARTHUR B. HYMAN: It is the description of lichen planus and not of necrobiosis.

DR. MARION B. SULZBERGER: The serologic reactions for syphilis were negative on two occasions.

DR. PERRY SACHS: This may well be a lichen planus. However, from the microscopic description, I cannot establish this diagnosis. Parakeratosis and involvement of the entire corium are not features of lichen planus.

DR. LOUIS V. LUTTENBERGER: This case in the beginning looked much more like a lichen planus than in the end, and we felt that the treatment with bismuth which was given was not sufficient and partially influenced the clinical appearance of the lesion.

Scrofuloderma and Tuberculous Sinus Treated Successfully with Isoniazid (Nydrazid). Acrodermatitis Chronica Atrophicans and Hyperpigmentation of the Skin Resembling Riehl's Melanosis. Presented by DR. MAURICE J. COSTELLO.

R. S., a Polish American housewife, aged 46, was seen for the first time by the presenter on Oct. 31, 1952, at which time she had a draining tuberculous sinus and scrofuloderma in the midsternal region, which had been present since a fixation operation (Albee) had been performed for tuberculosis of the vertebral column several years ago. There was a moderately profuse serosanguineous and seropurulent discharge, accompanied by pain, erythema, and edema of the tissues surrounding the sinus opening. Isoniazid (Nydrazid) was administered, 100 mg. three times a day. Beneficial therapeutic response was rapid, with amelioration of all the objective and subjective symptoms. There was no activity at this time. Weakness and dizziness were the side-effects of the drug.

She also has acrodermatitis chronica atrophicans of long duration, of unusual extent, and of moderate severity. It is severer on the right extremity. In addition to the diffuse involvement, there are discrete coin-sized areas of a ballooning type of atrophy. The hyperpigmentation is extensive, worse on the light-exposed areas and on the buttocks. Her mother and son have a similar but not as profound type of melanosis. The roundest areas of hyperpigmentation in the right lower thoracic region are due to x-rays.

DISCUSSION

DR. MABEL G. SILVERBERG: It is interesting that the patient responded to the therapy. Other similar successful reports with isoniazid in tuberculous sinuses have appeared in the literature. I thought that the pigmentation of the skin was interesting. The sclera seemed pigmented too, which would not be so in Riehl's melanosis.

DR. MAURICE J. COSTELLO: It resembles that.

DR. MABEL G. SILVERBERG: I wondered what other etiology there might be for the pigmentation. Argyria might be a possibility. Formerly, the sinuses were so often treated with silver nitrate. However, the skin, though slightly grayish, was a grayish brown.

DR. EUGENE BERNSTEIN: I cannot accept the diagnosis of acrodermatitis, as there are not sufficient symptoms to warrant such a diagnosis.

DR. NATHAN SOBEL: I also doubted the diagnosis of acrodermatitis when I looked at the lesion, but when I looked at the right elbow I saw that she has a very extensive area of atrophy, and I thought that the lesions around the right knee were in the infiltrative stages.

DR. HANS H. BIBERSTEIN: As to the diagnosis of acrodermatitis, I agree with what Dr. Sobel said. The lesions on the leg are typical. We see the infiltrative stage in which many plasma cells may be found histologically. As far as the pigmentation is concerned, the suggestion of Dr. Silverberg deserves serious consideration. In addition, since the patient has a history of tuberculosis of long standing, special attention should be paid to the adrenal glands, regarding the pigmentation (blood pressure, sodium chloride level, etc.). Another point would be to ascertain whether the intake and/or resorption of vitamin C was sufficient during all the years of her disease; we have known cases in which chloasma-like conditions have been ascribed to an apparent vitamin C deficiency and could be successfully treated by administration of high doses of ascorbic acid (vitamin C). (Sellei, J.: *Fortschr. Therap.* **11**:26, 1935; abstracted, *Zentralbl. Haut- u. Geschlechtskr.* **57**:27, 1936. Hoff, F.: *Deutsche. Med. Wchnschr.* **1**:129, 1936; abstracted, *Zentralbl. Haut.- u. Geschlechtskr.* **53**:549, 1936.)

DR. HELEN CURTH: I think that the fact that she was born in this country would also speak against acrodermatitis chronica atrophicans. Patients with this disease were almost all born on the other side.

DR. BEATRICE M. KESTEN: This is a rather remarkable case in that she has three different entities. I entirely agree with Dr. Biberstein on the tuberculosis and the pigmentation. The lesion on the right elbow is very typical of acrodermatitis chronica atrophicans. Biopsy of sections of this lesion and the pigmentation might be helpful. The presence of active tuberculosis should be sought.

DR. ALEXANDER A. FISHER: I believe that this patient has the infiltrative type of acrodermatitis atrophicans. I was somewhat surprised that penicillin treatment was not mentioned. In two cases recently observed, one patient did well and one failed to respond to penicillin. I should like to hear what others have experienced in the treatment with penicillin of acrodermatitis atrophicans.

DR. VICTOR H. WHITTEN: I should like to answer Dr. Fisher. As I have said previously in this section, many cases of acrodermatitis chronica atrophicans in which there has been treatment with penicillin have been reported in the literature. Thyresson of Sweden treated 57 patients, with good or excellent results in the majority of instances. I have treated six patients with this disease, using large doses of penicillin. The results were

very good in four of these patients. In addition, I have heard of other favorable reports. It should be understood, however, that there is response only in the symptoms and the infiltration; there is no alteration of the already established atrophy.

DR. MORRIS LEIDER: Is the successful treatment of scrofuloderma so banal that we devote the entire discussion to acrodermatitis atrophicans? What seems to me more important is the fact that the scrofuloderma was cured by isoniazid. We can confirm from experience at Bellevue that tuberculoderms that are characterized by the presence of tubercle bacilli in the lesions, e.g., lupus vulgaris, tuberculosis indurativa, and scrofuloderma, respond well and relatively quickly to isoniazid therapy.

DR. FREDERICK REISS: There is one remark I should like to make about the hyperpigmentation. I wonder whether Dr. Costello has paid attention to the number of articles which were published by Dr. Spiro, of London, England, Middlesex Hospital (*Schweiz. med. Wchnschr.* **14**:359, 1952), in relation to Riehl's melanosis and the involvement of the adrenal cortex due to chronic fluorosis. His findings have never been investigated in this country. Chronic fluorine poisoning is characterized by a hyperpigmentation, mottling of the teeth, and by a polyneuritis. I inquired whether the patient has polyneuritis, and the answer was negative; neither does she have mottled teeth. However, Spiro also described a number of cases in which these two features were absent. I should like to ask Dr. Costello if such an investigation can eventually be made.

DR. MAURICE J. COSTELLO: Someone said that I presented this case mainly to show the beneficial effects of isoniazid on a tuberculous sinus, which probably originated in the tuberculous vertebral bodies in tunneling along the rib and coming out in the sternal region, or from caseating tuberculous mediastinal lymph nodes. That is not infrequent. Or, it may have originated in the right hilum of the lung. This woman had a discharge from these sinus openings which was fairly profuse and serosanguineous and purulent in the beginning, and which has completely disappeared. The areas of edema pain surrounding the sinus opening had disappeared.

In regard to the hyperpigmentation that she presents, I think that it is familial, because her mother has it and her son has it, as I mentioned in my history—not as severe—but she said so much so that everyone comments on their hyperpigmentation, especially during the summertime. I do not think that there is anything missing to make a diagnosis of acrodermatitis chronica atrophicans. Any man in the first three months of dermatology would not hesitate to make the diagnosis. The patient has atrophy, wrinkling of the skin, and juxta-articular nodes which have been present for 20 years. What is missing?—the biopsy to confirm it.

Seborrheic Verruca of the Left Upper Quadrant of Abdomen of Two Years' Duration.

Presented by DR. PERRY SACHS, for DR. J. P. RUPPE JR. (by invitation).

A. S., a 70-year white man, was first seen on Nov. 26, 1952. He noticed a red scaly spot on his abdomen about two years ago. The patient applied no specific therapy, but when the lesion became painful and increased in size he sought medical attention. When first seen, the lesion was purulent and seemed granulomatous, suggesting a diagnosis of granuloma pyogenicum or a gumma. Upon treatment with 2% boric acid compresses and zinc oxide paste (Lassar's plain zinc paste) the superficial infection was controlled and the diagnosis of seborrheic verruca became more apparent.

Physical examination revealed the following findings: The patient presented an erythematous, oval, keratotic lesion, measuring about 3 by 2 cm. in diameter. The border appeared to be infiltrated and had a thickness of about 3 mm. The center of the lesion was not as raised as the periphery.

The Kahn test gave a negative result. The urinalysis showed normal results.

A biopsy report gave the following findings: The epidermis was greatly thickened, irregular, verrucous, and hyperkeratotic, and was arranged in a lace-like fashion, containing a horny cyst. The upper cutis showed dilated congested blood vessels and a reaction showing a great amount of pigment and chromatophores.

The diagnosis was traumatized seborrheic verruca.

DISCUSSION

DR. PERRY SACHS: The microscopic findings are characteristic of a seborrheic verruca. Clinically, I see the possibility of epidermoid carcinoma in situ of skin (Bowen's disease), but this is not substantiated microscopically.

DR. TIMOTHY J. RIORDAN: In spite of the report of biospy, I think we should entertain the diagnosis of epidermoid carcinoma in situ epithelioma.

Keloid. Presented by DR. MAURICE J. COSTELLO, for DR. WALTER G. GASNER.

L. S., 34-year-old Negro woman, presents many irregularly shaped tumor-like elevations. The patient states that since early childhood these growths developed after injuries; however, she exhibits several growths which appeared without prior injury. There is a similar tendency in the father and brother. Large tumor masses occurred on each ear lobe following the piercing of the ear lobes for earrings. These growths were surgically removed, without any reoccurrence. A large laceration on the forehead was not followed by any new growth. The patient had an elevated tumor removed from her back, removal of which was followed by x-ray therapy, and, subsequently, a much larger tumor growth developed in its place.

DISCUSSION

DR JOHN GROOPMAN: There is one very interesting feature. It seems that she was treated with x-ray, and she claimed that the keloid came back in that exact spot, but she felt that it was much larger than the original lesion.

DR. ANTHONY C. CIPOLLARO: When a patient presents himself with such extensive keloids one has a difficult therapeutic problem on his hands. The two large keloids on the side of the face are indeed disfiguring. I would not expect that safe quantities of x-rays or radium would have any effect on them. I would treat the face lesions by removing them either with the scalpel or with the cutting current and then I would irradiate the wounds while they are healing. If anything is going to cause these lesions to involute I think that the combination of surgery and radiation stands the best possible chance.

DR. H. GOODMAN: Is it too much to ask if Dr. Cipollaro in the last five years has had a similar instance in which a knife and x-ray gave a result he would be proud to bring us?

DR. ANTHONY C. CIPOLLARO: Oh yes!

DR. H. GOODMAN: Bring it around. I had the misfortune for a couple of years to receive postoperative cases from a surgeon. He had an extremely successful practice in Harlem. I am sorry to report that the results were very poor, despite efforts of Roentgen, Coolidge, and Edison. The keloids returned. Not one patient was happy with the result. Since then, I learned that the surgeon has retired and now lives in Miami.

DR. MAURICE J. COSTELLO: I think that the treatment suggested by Dr. Cipollaro has been successful in my hands, but I admit that the treatment of a keloid in a Negro is an entirely different proposition than the treatment of a keloid in a white man. I will say that at Bellevue Hospital we have treated a number of Negroes with keloid by the combined method (surgery and x-ray). It has been extremely difficult, but I have had very good results in treating white people by that combination method of therapy.

DR. GERALD F. MACHACEK: One must recognize that there are true keloids and pseudo-keloids. I think that Dr. Costello brought this out by implication. Hypertrophic scars may be keloidal. These hypertrophic scars tend to disappear spontaneously. Differentiation between these two conditions is often extremely difficult and often impossible.

DR. ANTHONY C. CIPOLLARO: I may have imparted the wrong impression. I do not cure every patient with keloid whom I treat—far from it. I simply state that the combination of surgery and radiation is probably the best approach to treatment of the facial keloids which this patient presents. I have had failures with that method, but I have also had successes.

DR. TIMOTHY J. RIORDAN: I believe that the time element is important in the differentiation that Dr. Machacek brought out. Most of these scar-tissue lesions that will offer or establish a differential diagnosis as between a hypertrophic scar and a keloid will do so after

a time. After six months it is more than likely that there will be changes of a particular degeneration in the keloid. In those cases all the x-ray that one can apply short of a destructive or caustic dose will have little or no effect on that degenerated tissue. On the other hand, with a combined method with the preventive dose of x-ray one will probably remove the excess in these young fibroblasts. As everyone well knows, the fibroblast is roentgen-sensitive, and that is the advantage of the combined treatment.

DR. MARION B. SULZBERGER: I should like to say a few words about this case, which I find very interesting and instructive. In the first place, there are keloids which are familial in incidence, and this is such a case. There are other people in the same family of this patient who have keloids. Is that not right?

DR. MAURICE J. COSTELLO: That is true.

DR. MARION B. SULZBERGER: Then there are the commoner keloids in which one can find no background of familial tendency. The next point is that there is not as much relationship between the severity of the trauma and the type of trauma and keloid formation as one might suppose. Sometimes, very inapparent traumas, like in this woman—the stretching of the skin during pregnancy—leads to keloid formation, whereas very severe and infected wounds do not lead to keloid formation in the same patient. My experience with x-ray in true keloids has been disappointing in the white race as well as in the Negro race. We have had men in the Navy in whom we have excised keloid after keloid and whom we gave every possible dosage of x-ray, without succeeding in preventing new keloidal scarring. Then again, for no apparent reason, sometimes keloids would not form when we excised the keloid without any x-ray at all. This case illustrates many of these points. For example, she had keloids excised from the ear without any renewed keloid formation and with a perfect cosmetic result. Therefore, I think that one of the conclusions that one must reach is that even in people with a strong tendency to form keloids the tendency is not always present, nor present at all sites. Sometimes keloids will form in these persons, but at other times, astonishingly enough, no keloid will form despite severely infected wounds. I remember very well a case of a young woman who had two types of abdominal injury, about a year or so apart. One was a suppurative wound from a gallbladder operation I believe, which had to be drained for a long time. No keloid formed there, despite the long-lasting infection and irritation of the wound. Then, only a short time later, the patient had a Caesarean operation, with a perfectly clean rapidly healing incision. This formed a huge keloid. So I think that in judging the usefulness of different kinds of treatment in keloids one must bear in mind the natural history of these cases and the mysterious fluctuations which these patients present in their tendency to form keloids.

DR. CHARLES LERNER: I am in complete accord with Dr. Cipollaro and Dr. Sulzberger. There are only two points that I would like to emphasize: One is that radium is preferable to x-rays, and, the other, that such radiation should be administered very soon after surgery. I think that most dermatologists are inclined to wait too long before instituting irradiation.

DR. GERALD F. MACHACEK: Nothing has been said about the possibility of a peculiar metabolic, enzymatic, or hormonal condition which affects the collagenous connective tissue. Is it possible that in keloids there is a lack of collagenase? The collagen bundles of keloids differ from those of normal tissue or hypertrophic scars.

DR. WALTER G. GASNER: I think that it is important to note that keloids did not develop in this patient after the surgical removal of two large keloids on either ear lobe. A keloid also did not form on the site of a large scar on the forehead, which was the result of a traumatic injury. One must assume that during various stages of development and age periods certain endocrine factors play a role in keloid development.

Tinea Tonsurans. Presented by DR. MAURICE J. COSTELLO, for DR. WALTER G. GASNER.

M. M., a white girl, aged 4 years, presents an eruption limited to the scalp, of five months' duration. There is a scaly patch on the left side of the scalp. The scales are flaky and white in appearance, with little or no loss of hair. Examination under the Wood's light revealed a dull whitish fluorescence. Direct microscopic examination of the hairs with KOH was

positive for fungi. Culture on Sabouraud's media revealed a velvety cream-colored growth with a central depression, with an older growth showing a crater formation. Microscopic examination of the culture showed numerous microconidia along the side of hyphae. Chlamydospores were found throughout the culture, with terminal swelling of the hyphae into club-shaped ends.

DISCUSSION

DR. MAURICE J. COSTELLO: Before Dr. Gasner closes, I should like to say that I think that this is one of the cases in which we see no fluorescence at all with the Wood's light, indicating that fluorescence with the Wood's light—and I need not tell this audience that—is not sufficient. Culture examinations must follow.

DR. ANTHONY C. CIPOLLARO: These cases of tinea tonsurans are being seen more frequently. I think that we have missed a good many of them because no fluorescence is seen. We depend too much on the Wood's light to identify fungus infection of the scalp. This is one type of scalp ringworm that could raise havoc in the district in which this child lives or the school she attends. These cases of tinea tonsurans are infectious and communicable and do not improve by themselves, not unless there is kerion formation or other inflammation. In such cases, the disease may involute spontaneously or may disappear after the use of topical remedies. The noninflammatory type is difficult to cure, even when treated with x-ray epilation. The rule is frequent recurrences. The secret of success lies in the patient removal of all hair stubs that look like black dots with epilating forceps before the hair begins to regrow. This requires hours of labor under a strong light. The stubs are loose in the follicles, but they will not come out by themselves. If the new hair grows back before all the infected stubs are removed, recurrence results. The manual removal of the hair stubs is an integral and important part of the therapy. Neither x-ray therapy alone nor manual depilation alone is apt to result in success.

DR. FREDERICK REISS: I do not believe that I can add very much to Dr. Cipollaro's discussion. I should like to make one short remark in relation to the mycological features. I believe that the fungus should be called Tricophyton tonsurans, and Tricophyton cerebriforme, Tricophyton acuminatum, and Tricophyton sulfureum are variants of this species. I fully agree with Dr. Cipollaro that one always should suspect a fungus infection when broken hairs are in the follicles, which as a rule do not fluoresce. The microscopic examination frequently shows a large spore endothrix fungus in such instances.

DR. ANTHONY C. CIPOLLARO: To complete the mycology, Dr. Reiss should have also mentioned T. sulfureum, which belongs to the same family.

DR. WALTER G. GASNER: The first time that this patient was seen at Lenox Hill Hospital, she did not present a perceptible loss of hair in the areas of involvement. The eruption appeared psoriasiform and much like a tinea amiantacea. Under the Hanovia Wood Light, there was no fluorescence except for the whitish color that one sees when keratin is exposed to the Wood light. Direct microscopic examination of the hairs revealed that they were positive for fungi. Culture on Sabouraud's media revealed a velvety cream-colored growth with a central depression. The diagnosis of tonsurans was established.

DR. MAURICE J. COSTELLO: Another point that ought to be brought out is that this is not an infrequent fungus infection in adults. It is often thought to be seborrheic dermatitis. Cases under treatment are often thought to be seborrheic dermatitis, and that fact was the experience of Pipkin. I think that since he emphasized that fact in his paper at the meeting of the American Dermatological Association we are more on the lookout for these fungous infections.

Lymphoma of the Upper and Lower Extremities and the Back of Five Years' Duration. Presented by DR. ANTHONY C. CIPOLLARO, for DR. M. ALDERMAN (by invitation).

B. L., a 59-year-old white man, first visited the skin clinic on Dec. 30, 1952. He states that he has been treated unsuccessfully during the past five years by his private physician. The lesions disappear almost entirely in the summer and become worse again during the winter months. Except for occasional mild pruritus, the patient has no other complaints.

No history of intake of drugs was elicited.

Laboratory examination gave the following findings: hemoglobin content, 16 gm.; red blood cells, 5,900,000; white blood cells, 9,925; with 75% polymorphonuclear leucocytes; 3% stab forms, 18% lymphocytes, 2% eosinophiles, and 2% monocytes.

The report of the biopsy gave the following findings: Throughout the cutis, the vessels were dilated and most of them filled with blood elements. There was a focal and somewhat diffuse reaction of fairly uniform cells. The reaction was composed of small round cells which suggested possible lymphocytes. An occasional mitotic figure could be seen. There were a moderate number of polymorphonuclear cells present. In some areas there was moderate interstitial edema in the upper cutis. The epidermis was mildly acanthotic and the drug and palisade margin intact.

The diagnosis was possible lymphoblastoma.

DISCUSSION

DR. ALEXANDER A. FISHER: There is one point that seems to be against the diagnosis of lymphoma, and that is that there are apparently spontaneous remissions in this dermatosis.

DR. PAUL GROSS: The statement of the patient that the eruption clears up in the summertime seems to be sufficiently reliable to be of some help in the diagnosis. The variety of lesions ranging from small lichenoid papules to typical psoriasiform patches and more infiltrated large lesions makes me think of the possibility of parapsoriasis with so-called varioliform lesions. The late Dr. Willy Pick published a case of parapsoriasis varioliformis with tumor-like lesions.

DR. MORRIS LEIDER: I agree with Dr. Gross.

DR. NATHAN SOBEL: I agree with Dr. Gross, and I want to add that one should consider also the question of drug eruption, because we have followed similar cases through the years that have been diagnosed similarly, and a rather large number of them turned out to be drug eruptions due to various drugs.

DR. FRANCES PASCHER: I am in accord with the diagnosis of parapsoriasis. However, the marked vascular element is rather unusual and atypical. The lesions are a vivid red and rather boggy—more inflammatory than one would expect to find.

DR. PERRY SACHS: The microscopic features are not particularly those of parapsoriasis. There is a strong suggestion of a possible lymphoblastoma. However, the possibility of a drug eruption as well as a prurigo nodularis could not be ruled out.

DR. JUAN LARRALDE: I made two rounds. The first time I only saw the arms of the patient, and I thought of parapsoriasis. The second time I saw the right upper leg near the abdomen. I found the lesion very infiltrated and nodular. We do not usually find that in parapsoriasis. Together with the histologic finding it could be taken as a lymphoma. It could be considered as a lymphoma.

DR. ANTHONY C. CIPOLLARO: I want to thank you all for the discussion. Some of the discussers are as confused as we are about the diagnosis of this case. We saw this patient for the first time last week. When we looked at him in our clinic we thought of psoriasis and of parapsoriasis. We seriously considered the diagnosis of lymphoma because of the nodular lesions which we found. These nodules are not found in patients with psoriasis or parapsoriasis, and when the pathologist informed us that the histology was consistent with a lymphoblastoma then we made a tentative diagnosis of lymphoma, with the idea of having the patient presented here and getting your opinions on his case. We shall make a further study of this case, which will include another biopsy, and we shall report the findings later.

DR. JOHN GROOPMAN: I should like to make one addition. I think that this falls in the parapsoriasis group. I feel that vitamin B_2 preparation should be tried during the height of his troubles, which is in the wintertime, pushed right to the fore, in high doses.

DR. ORLANDO CANIZARES: I am sorry I did not see the patient. It seems to me that the two diagnoses could be well solidified by some type of parapsoriasis. Some cases of this disease look like lymphoblastoma.

DR. MARION B. SULZBERGER: I do not think that this particular type of parapsoriasis is a forerunner of a mycosis fungoides or malignant lymphoma.

DR. ORLANDO CANIZARES: I did not see the patient.

DR. MARION D. SULZBERGER: It is a small papular type, a form of parapsoriasis *en goutte*.

Case of Multiple Superficial Hemangiomata, with Congenital Blindness of Left Eye.
Presented by DR. T. J. RIORDAN, for DR. JOSE G. REYES.

C. M., a 2½-year-old white girl, was born with more than 30 superficial hemangiomata, involving the face, neck, trunk, and arms. When the child was about 2 months of age, the mother noticed that the left eye appeared different from the right. Examination at that time revealed no vision of the eye. The hemangiomata were treated with carbon dioxide snow.

Ophthalmological consultation held two weeks ago revealed atrophy of the left eye, with thread-like arteries. The disc could not be seen clearly.

DISCUSSION

DR. MARION B. SULZBERGER: Would you agree with the diagnosis? retrolenticular fibroplasia. The child was born prematurely (6 months). Small hemangiomata with unilateral congenital blindness were present. I think that I would classify the case as that. I consider it one of the most interesting cases I have seen here this evening. It was very instructive.

DR. JOHN GROOPMAN: I think x-rays of the skull of this child should be done at the present time, because occasionally one finds the same hemangiomata as outcroppings of the vessels with impingement on the cranial vault itself. This can be seen by x-ray, especially at that age.

DR. MARION B. SULZBERGER: Would you agree with the diagnosis?

DR. JOHN GROOPMAN: Yes, I do, especially with the multiplicity of the hemangiomata and the universality of involvement.

DR. GERALD F. MACHACEK: That usually goes with the retrolenticular fibroplasia.

DR. JOHN GROOPMAN: The report that was in the *New York State Journal* several months ago mentioned the type of fibroplasia accompanied by the hemangiomata.

DR. GERALD F. MACHACEK: Several or one case?

DR. JOHN GROOPMAN: Several.

DR. MAURICE J. COSTELLO: I think that Dr. Rice at the Presbyterian Hospital did most of the work on this.

DR. HELEN CURTH: Is not this condition usually seen in both eyes, whereas in this child it is only in one eye?

DR. C. T. NELSON: In all the cases of retrolenticular fibroplasia seen at Presbyterian Hospital, the process has involved both eyes.

DR. T. J. RIORDAN: That diagnosis was considered. When the report from the eye department failed to confirm it, we thought that we would present it as a case for diagnosis.

DR. MARION B. SULZBERGER: There is nothing pathognomonic either in the eye or in the skin changes.

DR. MAURICE J. COSTELLO: I think there is. It is termed in the ophthalmologic examination—something in the history said thinning of arteries, thread-like arteries.

DR. MARION B. SULZBERGER: The report says, "revealed atrophy of left eye with the disc not seen clearly." Perhaps, Dr. Reyes, you can report on that case further.

DR. JOSE B. REYES: We ordered an x-ray of the skull, having in mind the possibility that in these cases there is involvement of the meninges, trigeminal nerve, and other intracranial structures. I should like to report next time what we find, and what the findings are in the literature.

NEW YORK DERMATOLOGICAL SOCIETY

George C. Andrews, M.D., *President*

Maurice J. Costello, M.D., *Secretary*

Jan. 27, 1953

Case for Diagnosis: Lupus Erythematosus? Erythema Perstans? Presented by Dr. Howard Fox.

J. F. H., a woman aged 36, had always tanned well. While she was in Florida for one month a year ago, an eruption appeared on the face, spreading to the chest, back, and arms the day after she left Florida. She had gone in swimming the day before and had smeared "Copper Tone" on the above-mentioned areas. The eruption has persisted in places up to the present. She again went to Florida a month ago and the eruption became worse the next day in spite of the long-sleeved sweaters and a large hat which she wore when exposed to the sun. She therefore had to return to New York three days later.

The eruption consists of ill-defined slightly raised pinkish smooth areas with a tendency to form circles on both malar regions and the flexor surface of the left arm. There are also about 10 discrete lesions on the back, the size of a small coin. The lesions seldom itch, and there are no scratch marks. Those on the face always look better a few days before menstruation.

A biopsy performed at the skin and cancer hospital showed no malignancy. The serologic reactions were negative, the erythrocyte sedimentation rate and the urine were normal, and the blood cell count showed 4,200,000 red blood cells and 15,000 white blood cells, with a normal differential count. Four x-ray treatments by another dermatologist had no effect on the eruption.

A mastoidectomy was performed 20 years ago and her left eardrum removed. Since then, the otologist has applied a powder consisting of iodine and boric acid to the left ear once a month. About two years ago the patient had a severe bronchial hemorrhage necessitating hospitalization for three weeks. Extensive examinations for tuberculosis gave negative results. She was found to have a labile blood pressure, ranging from 200/100 to 114/70. A cold-pressor test confirmed a neurogenic element in the blood-pressure fluctuations.

DISCUSSION

Dr. Wilbert Sachs: I thought that the patient had a recurrent erythema multiforme type of eruption belonging to the group of erythema perstans, most of which are drug eruptions.

Dr. Eugene F. Traub: The best diagnostic possibility is a superficial disseminated lupus erythematosus, although some of the lesions at present do not seem to conform. Drug eruption would be my second choice, but it is difficult to establish. The history of medication in the ears should be investigated, because it may have been changed over the years.

Dr. Paul E. Bechet: The lesions are characteristic of disseminated discoid lupus erythematosus. It is not infrequent, and of course lacks the internal manifestations of systemic lupus erythematosus, as well as its objective lesions.

Dr. George M. Lewis: From the polymorphous appearance one would think mostly of drug eruption, particularly since the rash is not typical for any other disease.

Dr. Leslie P. Barker: The polymorphous lesions and the extensive distribution are more in favor of a drug eruption than lupus erythematosus.

Dr. John C. Graham: The eruption has increased after exposure to the sun, which is suggestive of lupus erythematosus, although the appearance is more that of a drug eruption.

Dr. Howard Fox: I think that it is as likely to be lupus erythematosus as a drug eruption, although the fact that there were 15,000 white blood cells on one determination is against the former. There is no question that sunlight brought out the eruption on two occasions at least, although for many years the patient had been exposed to the sun in Florida, with no trouble.

Alopecia Prematura. Presented by Dr. Eugene F. Traub.

In P. E., a girl aged 17, a gradual loss of hair over the entire scalp began to develop at the age of 13. This was diffuse and general and at no time patchy. It followed no serious illness, but she was rather nervous. Some seborrhea was present. The general health seemed to be good. The patient's father was bald. The menses were painful, but otherwise normal. No focus of infection was found. Several basal metabolic determinations were within normal range. On

Feb. 11, 1952, a 17-ketosteroid determination was performed, and 2.73 mg. of 17-ketosteroids were excreted. The patient had taken internally and been given locally some female sex hormones. She was given large doses of vitamin B, liver, and, at various times, large doses of thyroid, stimulating treatment of the scalp in the shape of cold quartz lamp irradiation, phenol, and alcohol, etc. Despite therapy, the loss of hair has been slowly progressive. The best that can be said is that the process has been more or less arrested, but without any evidence of an attempt at hair restoration. There were never any pustules, nor has there been any suggestion of folliculitis decalvans, pseudopelade, etc.

The patient is presented because of the unusually early age of onset of generalized scalp alopecia in an apparently perfectly healthy and normal girl who has been thoroughly studied, without any ascertainable cause having been discovered. She is also presented for therapeutic suggestions.

DISCUSSION

DR. GEORGE M. LEWIS: Is there any history of heavy sun exposure? Has she ever been exposed to ultraviolet irradiation?

DR. EUGENE F. TRAUB: She got cold quartz ultraviolet light, but not before the alopecia developed, that I know of.

DR. PAUL E. BECHET: On close observation the scalp presented a pinkish hue, a shiny surface, and an extremely superficial type of atrophy. It suggests an anomalous type of very superficial alopecia cicatrisata. The above symptomatology is rare, but I have observed a few typical examples.

DR. MAURICE J. COSTELLO: I think that the patient has poor heredity as far as hair growth is concerned; all the uncles on her mother's side were bald at an early age. I believe that this represents alopecia at an early age, as we see in young men, hereditary in type, and that there is nothing to do about it. It will probably be progressive. I have seen it occur at the age of 16.

DR. GEORGE C. ANDREWS: I was interested in her wisdom teeth, because we have reported cases like this due to impacted wisdom teeth. She has 4 impacted wisdom teeth, and I should like to have them out.

Mycosis Fungoides: Remission After Corticotropin Therapy. Presented by DR. GEORGE M. LEWIS.

In O. F., a man aged 59, a dermatitis of the face developed two years ago. He also presented ill-defined scaly red lesions on the trunk. A diagnosis of seborrheic dermatitis was made. A year later, in January, 1952, the presenting eruption included infiltrated plaques and diffuse redness and involved widespread areas on the extremities, trunk, and face. Itching was intense. Normal skin could be seen between the affected areas. He had been observed at Roosevelt Hospital, and biopsy there suggested mycosis fungoides. He received a moderate amount of x-ray therapy. He was under the private care of Dr. Leonard Kornblee from May to December, and during that time he received conservative x-ray therapy, stibophen (Fuadin), liver extract, and various other remedies.

Examination in December revealed the tumor stage of mycosis fungoides, with beginning ulcerative nodular lesions and heavily infiltrated plaques. Biopsy confirmed the clinical impression.

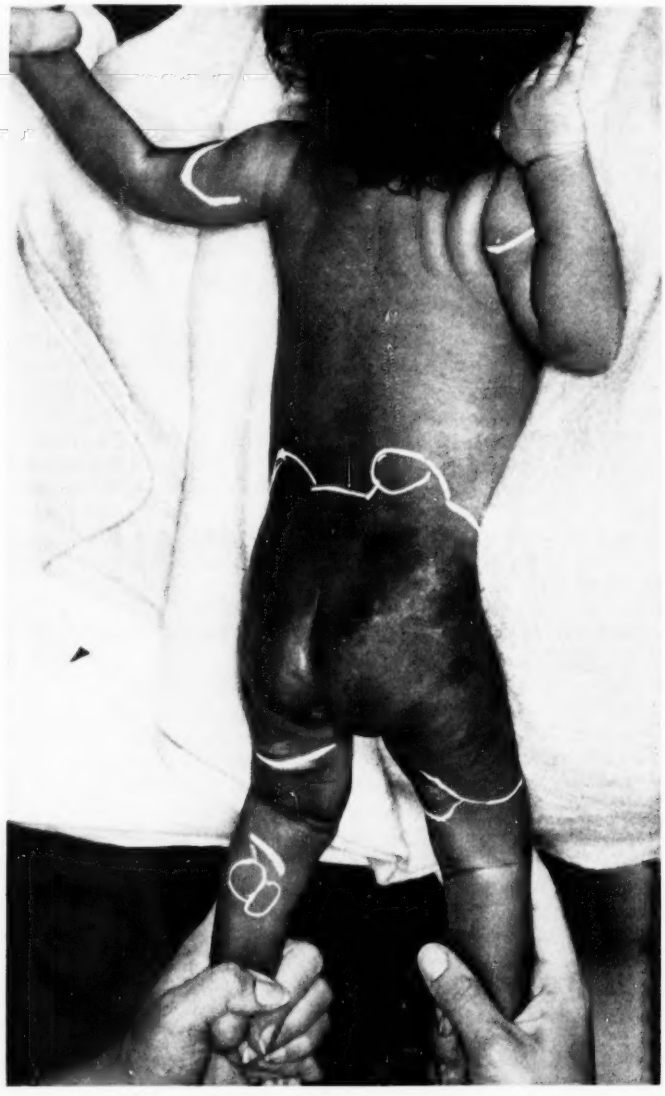
On Jan. 7, 1953, corticotropin (ACTH) therapy was begun, 40 mg. daily, with five injections a week. In one week a remarkable flattening of the eruption occurred. He has had 15 injections to date.

DISCUSSION

DR. CARL T. NELSON (by invitation): There is no doubt that mycosis fungoides will occasionally be benefited temporarily by corticotropin or cortisone. However, in the few patients we have treated the results have been quite transitory. I think that this man's prognosis is gloomy, and that he cannot be given corticotropin for any great length of time.

DR. ANTHONY C. CIPOLLARO: In extensive cases such as this, I think that any therapeutic agent that helps is the one to use. From what we heard tonight, corticotropin has done the man a great deal of good, and as long as it causes involution of lesions I would go on with

the therapy. I am sure that Dr. Lewis will do everything possible to prevent the severe complications that result from administration of the steroids, but as long as the patient shows improvement I think he should continue the corticotropin therapy.



Sclerema neonatorum? Subcutaneous fat necrosis?

DR. MAURICE J. COSTELLO: I wonder if the patient has had sufficient x-ray treatment? That is still a good treatment for mycosis fungoides. I would be inclined not to use corticotropin, because its effect is transitory and it is toxic at times.

DR. GEORGE C. ANDREWS: Everybody has spoken wisely and truthfully. At present, the drug is helping. He is in such bad shape that it is wise to go on, but the effect is going to be transitory.

DR. GEORGE M. LEWIS: As mentioned in the history, this patient had tumors with ulcerations, and if you had seen him then you would realize that tonight, although he is not cured or anywhere near well, he is perhaps 80% better than during that period. X-ray therapy had been given to tolerance, so the problem was to find a remedy. His case is certainly not presented as a cure, but as a partial remission, and I thought that the case was of interest because of the small dose administered. One would hardly think that there was danger of reaction to doses of 40 mg. five days a week. So far there is no sign of drug reaction.

NOTE.—Two weeks after presentation, tumors were again developing, accompanied by intolerable pruritus.

Erythema Induratum Type of Eruption. Presented by DR. LESLIE P. BARKER.

Case for Diagnosis: Purpura? Cutaneous Manifestations of Infectious Mononucleosis? Presented by DR. ANTHONY C. CIPOLLARO.

Squamous-Cell Epithelioma of the Lower Lip, Treated Successfully with X-Rays. Presented by DR. MAURICE J. COSTELLO.

Osteomatosis. Presented by DR. GERALD F. MACHACEK.

Case for Diagnosis: Sclerema Neonatorum? Subcutaneous Fat Necrosis? Presented by DR. LESLIE P. BARKER.

Case for Diagnosis (Lipoid Proteinosis, Lipoidosis Cutis, [Sine] Mucosae). Presented by DR. MAURICE J. COSTELLO.

Chronic Porphyria. Presented by DR. J. LOWRY MILLER.

Granular Cell Myoblastoma. Presented by DR. GERALD F. MACHACEK.

Lupus Erythematosis of Fixed Type Associated with Diabetes Mellitus, Improved by Calcium Pantothenate. Presented by DR. MAURICE J. COSTELLO.

Erythema Annulare Centrifugum. Presented by DR. J. LOWRY MILLER.

George C. Andrews, M.D., *President*

Maurice J. Costello, M.D., *Secretary*

Feb. 24, 1953

Case for Diagnosis (an Unusual Form of Erythema Multiforme Confined to the Upper Respiratory and Possibly to the Digestive Tract?) Presented by DR. MAURICE J. COSTELLO.

E. T., a boy aged 5, has had recurrent erosive bullous lesions on the tongue, soft palate, buccal mucous membranes, and possibly on the trachea and bronchi as well as in the intestinal tract, for the past eight weeks. The crop of blisters have often been associated with fever, the temperature ranging between 101 and 105 F, with the child being extremely nervous during this time. All forms of therapy have been used to no avail, including cortisone, corticotropin (ACTH), oxytetracycline (terramycin) by mouth, chlortetracycline (aureomycin), and local medications. The child appears emaciated; he weighs only 38 lb. (17.2 kg.). He is a high-strung, nervous child who continues to pick his skin, especially on the right tragus, where he has produced an excoriation on the left side of his face, and on the umbilicus. When seated on his father's lap, he picks the tragus of his father's right ear. I understand that his mother also has a tendency to pick her lips. In addition to the fever, this child had a cough accompanied by expectoration of a stringy type difficult to produce in sufficient quantity to have a specimen examined. There were erosions of the dorsal aspect of the tongue distal to the angle of the circumvallate papillae and on the tip and right side of the tongue; there were ruptured bullae on the soft palate and on the buccal mucous membranes. The trachea and bronchi were not examined, but I believe that there were probably similar but milder lesions present and that the gastrointestinal tract was also involved.

The most recent treatment which offers a promise of success has been the administration of 25 mg. of chlortetracycline by mouth four times daily, with injections of large doses of panvitamin preparations. This child has been unable to eat solid or semisolid foods, so that his diet has

consisted of a concoction of Dryco (dried whole and skim milk with vitamins A and D), ice cream, eggs, and milk, which has served to maintain his nutrition. The child now appears to be getting well.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: My impression is that the lesions are of toxic and presumably infectious origin because of the child's temperature reading. I think that the nutritional changes are secondary to the fact that he cannot eat. In the broad sense, it could very well be included as one of the aberrant manifestations of ectodermosis erosiva pluriorificialis (Stevens-Johnson syndrome).

DR. FRANK E. CORMIA: I agree with Dr. Cipollaro.

DR. PERRY SACHS (by invitation): Usually erythema multiforme is recurrent. I believe that the child has had this continuously, which is not usual in this type of erythema multiforme.

DR. EUGENE F. TRAUB: A number of interesting features should be further investigated. One, for instance, is the allergic angle. We do not know what this child uses as a laxative. He had a small lesion on the lip that did not suggest it, but some of the larger lesions on the tongue might conceivably be due to phenolpthalein. Local contact in the mouth is something else to be considered, and a third possibility is that the eruption is due to some internal disorder, maybe one of the virus infections now prevalent. The idea of ectodermosis erosiva pluriorificialis is of course another angle.

DR. J. LOWRY MILLER: The recent response to chlortetracycline would speak more in favor of an aberrant form of ectodermosis erosiva pluriorificialis.

DR. GEORGE C. ANDREWS: I would not like to label it ectodermosis erosiva pluiorificialis without further study. The fever might represent something that has been missed internally. Infectious mononucleosis is not easy to diagnose, nor is Hodgkin's disease. I have never seen lesions on the tongue of this type in so young a child. I think we have to keep our minds open and not label the case until we are more sure.

DR. MAURICE J. COSTELLO: I would rather think that it is a type of erythema multiforme, not necessarily ectodermosis erosiva pluriorificialis, because I have never seen a case in which the eyes were not involved as well, and this child has a sufficiently severe eruption to bring about involvement of the eyes. It is not unusual to see erythema multiforme associated with tracheobronchitis. It may be of virus causation. He has had every study by excellent physicians. I think that the child responded best to chlortetracycline, which is the drug of choice for treatment of erythema multiforme of the recurrent type and which has little value in ectodermosis erosiva pluriorificialis. The possibility of drugs as an etiologic factor has been ruled out completely.

Case for Diagnosis (Macular Atrophy Secondary to Chronic Pyoderma? Presented by DR. ANTHONY C. CIPOLLARO.

M. A., a girl aged 12, was first seen by me on Jan. 29, 1953. It was stated that when she was at the age of 9 an erythematous eruption appeared on the buttocks about the time of onset of the menses. At that time, the patient also suffered from swelling of the knees. The eruption persisted. One year ago lesions appeared on the elbows and lower extremities. They were described as pustules or small blisters, which became infected and bled. Scarring occurred after their involution. At times there was concomitant swelling of the elbows, wrists, and knees.

The patient had been the subject of investigation in several hospitals and clinics in this city. Treatment had consisted of oxytetracycline (Terramycin) and erythromycin orally, and bacitracin and neomycin topically. High-vitamin, iron, and high-protein therapy had been attempted. Cortisone had failed to improve the lesions. Biopsy from a necrotic lesion on the right leg was done in December, 1952, and the specimen was diagnosed as acute inflammation—abscess. Complete blood cell count, lipid and liver function and blood clotting studies gave essentially normal results. The diagnosis of extracellular cholesterosis had been entertained.

The patient presented multiple circular and elliptical lesions varying from small to large coin-sized, scattered on the elbows, buttocks, anterior and posterior thighs, and scattered areas of

the trunk. More recent lesions were elevated, hemorrhagic, crusted, and, in some instances, pustular. The older lesions presented a wrinkled atrophic surface, elevated in some instances and flat in others. Some of these lesions could be invaginated.

The case is presented for diagnosis and suggestions for treatment.

DISCUSSION

DR. FRANK E. CORMIA: I am in agreement with Dr. Andrews; I believe that it is a borderline case of pyoderma gangrenosum and that antibiotic treatment should be combined with measures to improve the general health. With prolonged therapy, injections of liver, high-vitamin diet, etc., I think that complete cure will be obtained.

DR. GEORGE M. LEWIS: There is a peculiar tendency to form a ballooning type of scar, and I have never seen this in pyoderma.

DR. DOUGLAS P. TORRE (by invitation): I agree with Dr. Lewis. There is probably an elastic-tissue deficiency. With distribution of the atrophic lesions over points of friction, I thought of Ehlers-Danlos syndrome. The pustules are probably secondary to injury of the skin at these points of repeated trauma.

DR. WILBERT SACHS: To me it appeared as a peculiar form of macular atrophy. Biopsy would be very helpful. If there is fibrosis, one could rule out macular atrophy; if fibrosis is not present one would have to entertain that diagnosis.

DR. PAUL E. BEHCET: A few of the lesions are nummular in configuration and bluish-white in color. Some can be inverted with the finger, a common occurrence in the anetoderma of Schweninger and Buzzi, yet others bear some resemblance to acne conglobata. The clinical diagnosis is therefore not definite.

DR. MAURICE J. COSTELLO: I have never seen that vaccinoid type of ballooning in macular atrophy. I would be inclined to believe that the child is extremely susceptible to some type of organism. The question of colitis should be investigated, as many cases of pyoderma gangrenosum are associated with colitis.

DR. EUGENE F. TRAUB: I think that the patient has the disease that has been variously reported as acne aggregata seu conglobata, pyoderma gangrenosum, etc. The lesions described occur particularly in young girls in these areas, the scars being either of the balloon or keloidal variety. In true acne conglobata there are supposed to be comedones, but some of the other names attached to the disease have been given simply because the acne comedone has not been present. The textbook picture in Ormsby and Montgomery is exactly like the one this patient presents: The eruption fits into this category, whatever the disease.

DR. J. LOWRY MILLER: I agree with Dr. Traub regarding the diagnosis. I would suggest that the organism be tested for sensitivity to various antibiotics. I have an idea that it would be resistant to most of them and susceptible to only one or two.

DR. EUGENE F. TRAUB: Very extensive laboratory work was reported by Ormsby, and the findings were either Staphylococcus albus or some acne bacillus. The organism is not the same in each case, and the response to antibiotics is not particularly good.

DR. GEORGE C. ANDREWS: There is not a great deal of difference between acne agminata, acne conglobata, and pyoderma gangrenosum. I agree with Dr. Miller that the case should be studied further; sensitivity tests to the various antibiotics are very important, for some Staphylococcus or low-grade infection is the basis of this disease. I believe that the best diagnosis is pyoderma gangrenosum with echthymatiform scars.

DR. FRANK E. CORMIA: The scarring, as Dr. Traub implied, is not only atrophic, but keloidal as well.

DR. ANTHONY C. CIPOLLARO: The girl presents a real diagnostic problem. I am inclined to feel that infection plays a role. The active infected areas which she now has could be labeled pyoderma, but certainly not acne conglobata. There may also be present evidence of a development defect. We all know that in Ehlers-Danlos syndrome infections appear at sites of scars. However, this patient does not have hyperextensibility of the fingers or elasticity of the skin, although she does have the type of atrophic scarring that is seen in Ehlers-Danlos syndrome. I shall perform bacterial sensitivity tests. Apparently no one thought seriously that it might be extracellular cholesterosis.

REPORTS FROM PREVIOUS MEETINGS

Lymphoblastoma (Mycosis Fungoides?). Presented by DR. FRANK E. CORMIA.

DR. FRANK E. CORMIA: A patient was presented last year for diagnosis (Lymphoblastoma [Mycosis Fungoides?] A.M.A. ARCH DERMAT. & SYPH. **66**:658, [Nov.] 1952), and the consensus was mycosis fungoides. At that time it was agreed that the diagnosis was lymphoblastoma, probably mycosis fungoides, and it was thought that the disease might eventuate into some other type. The patient was treated with fractional x-rays, and the lesions of mycosis improved nicely. There were a few reddish-brown spots on the extremities which were considered senile angiomas or some other unrelated lesion. The patient lost weight and strength after the cutaneous lesions had improved, was hospitalized at Memorial Hospital, and died. Autopsy showed extensive multiple hemorrhagic hemangioma of Kaposi with internal lesions.

DR. EUGENE F. TRAUB: I believe that it must have been merely a coincidence for multiple hemorrhagic hemangioma of Kaposi to have been present.

DR. WILBERT SACHS: I believe that six cases of coexistent multiple hemorrhagic hemangioma of Kaposi and lymphoblastoma have now been reported. On the basis of six or possibly seven cases I do not believe that one can assume that multiple hemorrhagic hemangioma of Kaposi belongs to the lymphoblastoma group.

Lichen Ruber Moniliformis. Presented by DR. PAUL E. BECHET, Elizabeth, N. J.

I presented a patient with lichen ruber moniliformis before this Society on Feb. 26, 1952 (A.M.A. ARCH. DERMAT. & SYPH. **66**:654, 1952) because of the excellent results of treatment with cortisone acetate in doses of 25 mg. three times a day. The eruption at the time of presentation had so improved that it was difficult to make a diagnosis, despite the fact that the lesions had been typical and quite severe before cortisone (Cortone) therapy. I saw the patient a month ago and she is entirely well, despite the fact that cortisone therapy had been discontinued for 10 months. Dr. Lewis, in his discussion, stated that apparently this case was the first in which there was treatment with cortisone. The drug was used experimentally, as everything else had failed to have any effect whatsoever on this rare dermatosis.

Alopecia (Roentgen? Areata?). Psoriasis. Presented by DR. GEORGE M. LEWIS.
Porokeratosis of Mibelli. Presented by DR. LESLIE P. BARKER.
Pigmented Nevus. Presented by DR. WILBERT SACHS.
Urticaria Pigmentosa. Presented by DR. J. LOWRY MILLER.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Ferd D. Weidman, M.D., *Chairman*

Bertram Shaffer, M.D., *Secretary*

Jan. 16, 1953

Xanthomatous Biliary Cirrhosis. Onychomycosis. Presented by DR. CARMEN C. THOMAS and (by invitation) DR. JOHN YEAMAN.

C. T., a white woman, aged 37, presented a distended abdomen, enlarged liver, free fluid in the abdomen, enlarged heart, left pleural effusion, and hemorrhoids. There were slightly elevated sharply demarcated yellowish-brown periorbital plaques. Similar lesions were present on the neck in a retiform arrangement. There was marked palmar erythema, with erythematous scaly slightly elevated sharply circumscribed round lesions on the right elbow and the dorsum of the left hand. The nails showed marked thickening of the free edge.

The patient had had eight admissions to the Philadelphia General Hospital for xanthomatosis and biliary cirrhosis.

The complete blood cell count revealed 8.6 gm. hemoglobin content, 5,800 leucocytes, with 57% neutrophiles, 35% lymphocytes, 5% monocytes, and 5% eosinophiles. Prothrombin time determination was 37%. The Schilling count showed 8 bands, 49 segmented. The blood sugar was 81 mg. per 100 cc., urea 25 gm., and alkaline phosphatase 11.45 mg. The Kolmer Wassermann reaction of the blood for syphilis was negative. Urinalysis gave normal findings.

On Aug. 25, 1952, the total blood cholesterol was 406 mg. per 100 cc.; cholesterol esters, 135 mg.; bilirubin, 2.77 mg.; prothrombin time determination, 93%; protein, 7.6 gm.; albumin, 3.2 gm., and globulin, 4.4 gm.

On March 11 the blood cholesterol was 280 mg. per 100 cc.; cholesterol esters, 35 mg.; phospholipids, 295 mg.; neutral fat, 46 mg.; total fat, 685 mg., and total fatty acids, 400 mg.

On March 6 cephalin flocculation was 4 +; thymol turbidity, 7.3, and thymol flocculation, 3 +.

Regression of Nodules of Xanthoma Tuberosum with Pressure Dressings. Presented by Dr. Thomas Butterworth, Reading, Pa.

This case will be discussed in full in a future issue of the A. M. A. Archives of Dermatology and Syphilology.

DISCUSSION

Dr. Thomas Butterworth, Reading, Pa.: This patient demonstrates one of the oldest principles of pathology, namely, that constant pressure leads to atrophy, in contrast to intermittent pressure, which leads to hypertrophy. As children you were impressed by the stories of Chinese women who strapped their feet to make them small. Then, later, in medical school, those of you in middle or late life remember the examples of corset liver that were shown to us, because in the early part of the century the girls wore a tight belt around the upper abdomen, and constant pressure led to a definite depression across the liver. You also recall hearing in those same pathological discussions how a fast-growing tumor would press against glandular tissue and lead to atrophy. Later, when you became dermatologists and interested in the skin, you began to see many examples of the effects of chronic, prolonged pressure. Now, the most striking of these, of course, is the decubitus ulcer. The pressure in that particular instance is of such intensity and duration that gangrene results. But in examples such as this tonight, we are interested in pressure of insufficient intensity and duration to cause gangrene. A fine example of the effect of such pressure occurs under the nose pads of your glasses. You have all seen the deep pits on the sides of the upper part of the nose. You have also seen the deep pits that develop under the pads of trusses in elderly people who have worn trusses for twenty or thirty years. These are examples of chronic, constant pressure. Another example of the effects of prolonged, constant pressure may occur under the garters of women. I am sure that all of you have seen the deep grooves around the lower thighs produced by garters. I am not certain whether that is really a pressure atrophy or whether it is a failure of fat to be laid down under pressure. Most of the women who show that are heavy and are usually middle-aged or elderly. It may be that under the garter we see the same phenomenon that takes place under the wedding band—the fat in the tissues does not increase in regions of constant pressure.

Now, as to the clinical application of these results—there is not too much written about it. I was unable to find any reports of the histologic changes taking place under the pads of glasses or under the pads of trusses. Ophthalmologists and surgeons, top-flight men, could not give me any help from the laboratory and experimental point of view. They have done some work with pressure on the tails of rats. Here, if pressure is applied insufficient to produce gangrene, one notes hyperplasia of the epiderm, muscle degeneration, and, finally, fibrosis of the muscles. Under some circumstances, a whole tail can become a fibrous thread.

This patient implanted the idea about this pressure business in my head because after he had done some really hard work in which picks and pipe wrenches were involved, he said (referring to his xanthoma), "Look, my hands are getting better. Hard work agrees with me." We put on the Elastoplast bandages. At first, improvement was rapid; then later we had to put the pieces of inner tube over the pads in order to increase the amount of pressure. He has done very well, and there is nothing left in the swelling on the left knee except fibrous tissue.

I have another patient whose lesions were principally on the elbows. His lesions have regressed about one-third with pressure dressings.

Naturally, we would like to apply this technique to other things. Dr. German and I have applied pressure dressings on a number of keloids and we feel that, if properly applied—and it is not an easy matter to apply these dressings in such a manner as to make them stick for a week—they will decrease in size. I have a private patient who has been coming back for pressure

dressings for about six weeks and is happy to do so. Another possibility that came to mind is treating the angiomata with pressure dressings. Of course, many of these are not in a location which will lend itself to such treatment. In several cases in which I have been able to apply the pressure dressings, the results have pleased the patients and me very much.

Ocular Pemphigus. Presented by DR. JOSEPH V. KLAUDER.

Case for Diagnosis. (Possible Variant of Granulosis Rubra Nasi?). Presented by DR. H. H. PERLMAN and (by invitation) by DR. M. M. CAHN.

Periarteritis Nodosa? Dermatomyositis? Presented by DR. CARMEN C. THOMAS and (by invitation) by DR. JOHN YEAMAN.

Discoid Lupus Erythematosus. Presented by DR. CARMEN C. THOMAS and (by invitation) by DR. JOHN YEAMAN.

Epidermolysis Bullosa-Dystrophic Type. Presented by DR. MARJORY K. HARDY and (by invitation) by DR. JOHN YEAMAN.

Granuloma Inguinale. Presented by DR. MEYER L. NIEDELMAN and (by invitation) by DR. JOHN YEAMAN.

Granuloma Inguinale, Treated on Ambulatory Basis. Presented by DR. MEYER L. NIEDELMAN and (by invitation) by DR. JOHN YEAMAN.

Disseminated Discoid Lupus Erythematosus. Presented by DR. CARMEN C. THOMAS and (by invitation) by DR. JOHN YEAMAN.

Basal-Cell Epithelioma. Presented by DR. CARMEN C. THOMAS and (by invitation) by DR. JOHN YEAMAN.

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Case for Diagnosis—Mycosis Fungoides? Presented by DR. HERBERT M. LEAVITT.

Lymphoma Cutis? Presented by DR. ADOLPH H. BLEIER.

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X-Ray Dermatitis Occurring After Treatment for Lupus Erythematosus. Presented by DR. ADOLPH H. BLEIER.

Mycosis Fungoides. Presented by DR. JOHN W. LENTZ.

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Xanthoma. Presented by DR. CARMEN C. THOMAS and (by invitation) by DR. JOHN YEAMAN.

Obituaries

HARRY E. ALDERSON, M.D.
1877-1952

Harry E. Alderson, long-time Professor of Dermatology at the Stanford University Medical School, died on Dec. 13, 1952, after a long and distinguished career.

Dr. Alderson was born in Dixon, Calif., on Dec. 18, 1877; his parents soon after moved to Healdsburg, and there young Alderson's early boyhood was spent. Later came a second move, this time to the Hayes Valley district of San Francisco, where he attended the public schools.

He received his medical degree from the University of California Medical School in 1900 and began a professional career that was to continue until his last illness more than half a century later. After several years in general practice, he became an assistant in dermatology at the University of California, serving under the late Dr. Douglass Montgomery. In 1907 he studied under Dr. Fordyce at Bellevue Hospital and under Dr. George Henry Fox at the Vanderbilt Clinic. He also studied under Professor Bowen at Harvard Medical School and Professor Gilchrist at Johns Hopkins. In Europe, in 1911 and 1912, he continued his studies under Professor Arndt, in Berlin, Professor Gaucher, in Paris, and Sir Ernest Graham-Little, in London.

Returning to San Francisco late in 1912, he was selected by Dr. Ray Lyman Wilbur to be Professor of Dermatology and Syphilology and chief of that department at the new Stanford University Medical School, which had recently taken over the Cooper Medical School. This position he held for thirty-two years until his retirement in 1944.

Throughout his career his professional interests were broad and his activities many. He served the San Francisco County Medical Society in numerous capacities. He was secretary during the trying days of the fire and earthquake of 1906, and it was in response to his call that the first meeting was held after the disaster. He long continued as a director of the society and served as its president, beginning in 1920.

From 1912 to 1926 Dr. Alderson was continuously a member of the State Board of Medical Examiners and was for a time its president. He was also a director and past president of the San Francisco Pan-American Medical Society and—in a somewhat different field—of the Society of Medical Friends of Wine, of which he was one of the founders.

His hospital staff appointments included Stanford University, St. Mary's, and Notre Dame. He was a one-time chief of the dermatology department of the Franklin and Chinese Hospitals and for many years consultant in dermatology at the San Francisco Marine Hospital and Samuel Merritt Hospital in Oakland. He likewise served as chief dermatologist at the San Francisco County Hospital, the Laguna Honda Home, and the Infant Shelter. During World War I he was consultant in dermatology at the Letterman General Hospital.

Dr. Alderson took a leading part in the planning and building of the Medico-Dental Building in San Francisco. In 1924, as president of the board of directors,

he turned the first shovelful of earth on the site at ceremonies marking the beginning of construction. He remained a director until the time of his death.

His numerous society affiliations included membership in the American Dermatological Association, the American Academy of Dermatology and Syphilology, the Society for Investigative Dermatology, the California Academy of Medicine, the San Francisco Dermatological Society, the Pacific Dermatologic Association,

HARRY E. ALDERSON, M.D.
1877-1952

and the American Medical Association. On the social side he was a member of the Bohemian and Olympic Clubs and of the San Francisco Golf Club. He was also a member of the Nu Sigma Nu fraternity and the Commonwealth Club.

His writings on dermatology were extensive, totaling more than seventy published papers.

In 1905 Dr. Alderson married Cordelia Bishop, of the prominent Honolulu family. One daughter, Mrs. Frank De Forrest, survives him.

Dr. Alderson continued active practice until his entrance into the Stanford University Hospitals in July, 1952. His death five months later brought to a close one of California's most distinguished medical careers.

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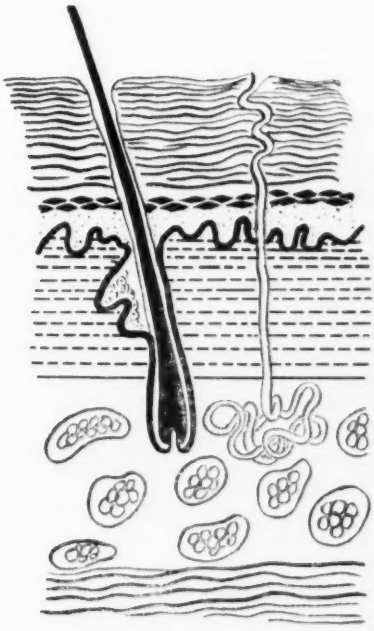

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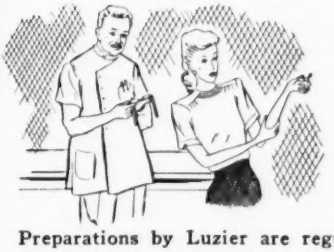

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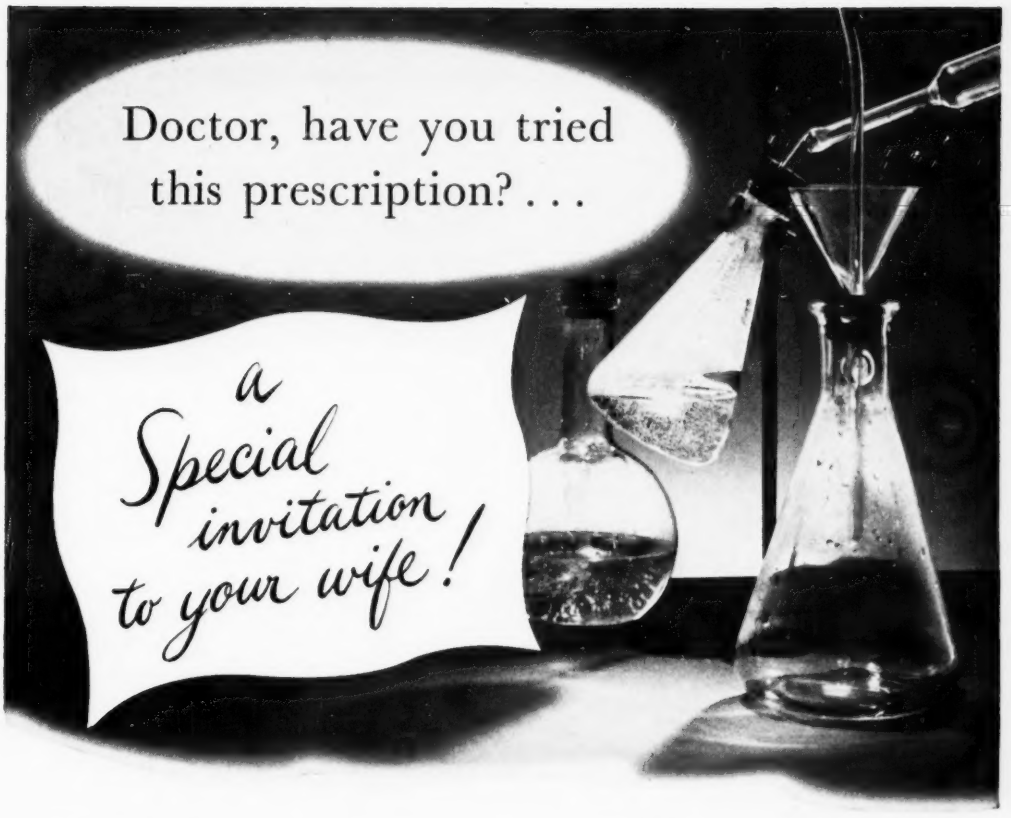

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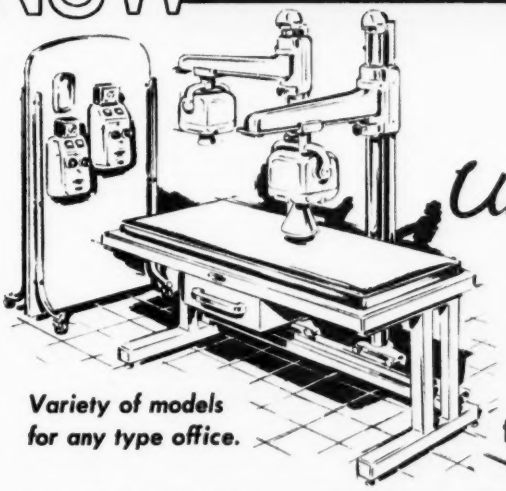

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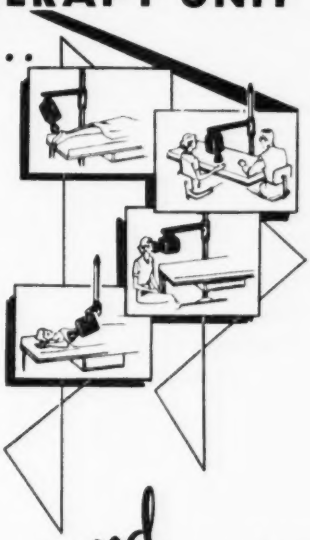

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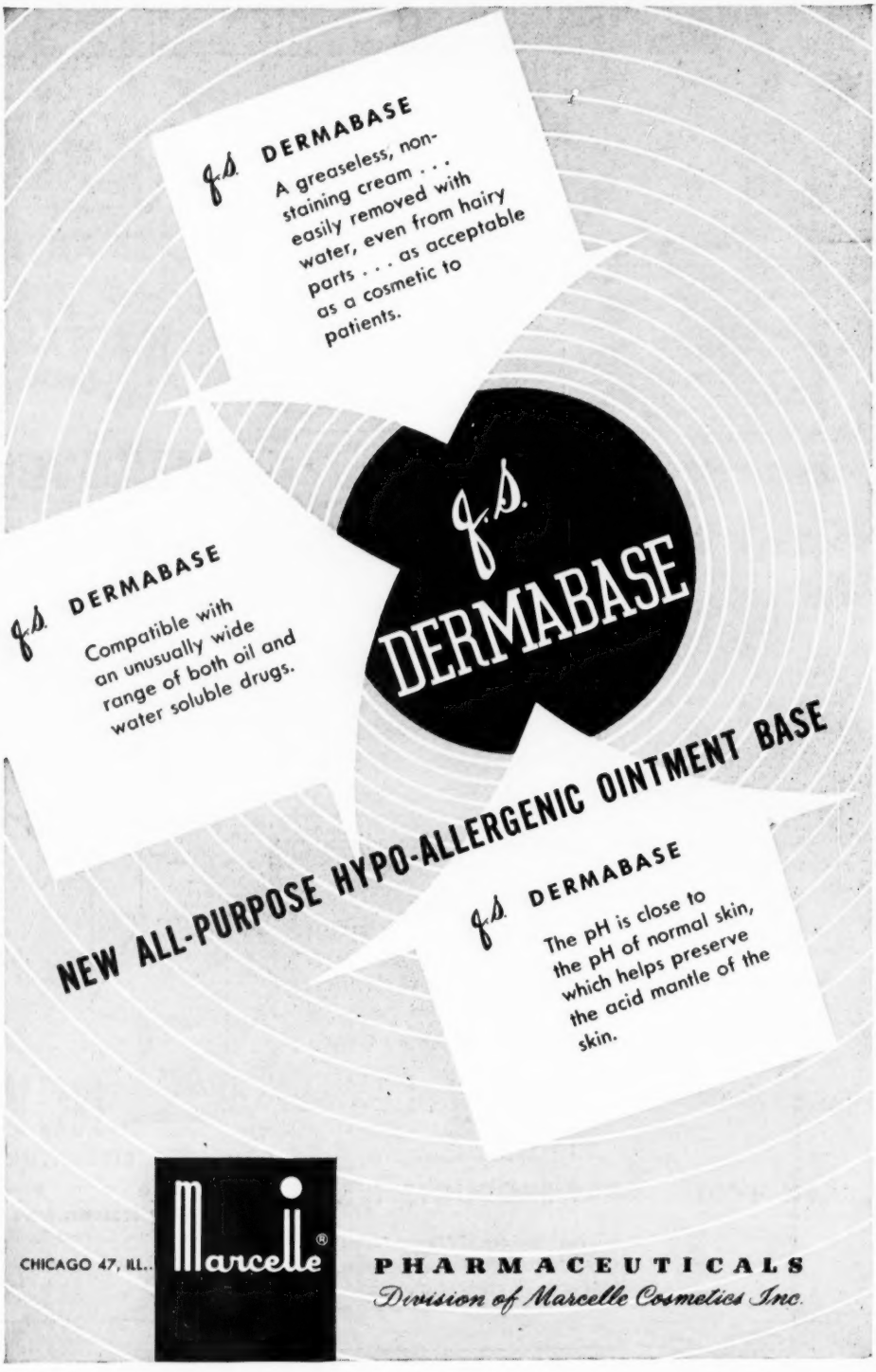
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